COUNTWAY LIBRARY
HC 3117 W

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE
HARVARD MEDICAL LIBRARY-BOSTON MEDICAL LIBRARY

Digitized by the Internet Archive
in 2016

https://archive.org/details/westernjournalof1524cali

DISPLAY SHELVES

INCORPORATING ZONA DICINE

SEE PAGE 376

# The Western Journal of Medicine

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE BOSTON, MA APR 20 1990

VOLUME 152 • NUMBER 4 APRIL 1990


**CLINICAL MEDICINE**

377 Physical Diagnosis Versus Modern Technology—A Review
F T FITZGERALD

383 Current Management of the Wolff-Parkinson-White Syndrome
A ARAI and J KRON

**MEDICAL PROGRESS**

392 Perspective on Hypertension in the Elderly
B WHITCOMB and R L BYYNY

**MEDICAL STAFF CONFERENCE**

401 Immunotherapy for Infectious Diseases
Discussant: J E PENNINGTON

**EPITOMES**

406 Important Advances in Obstetrics and Gynecology

**EDITORIALS**

414 Three Possible Futures for Medicine • Hypertension in the Elderly

**CASE REPORTS**

417 Erythrocytosis Caused by an Erythropoietin-Producing Breast Adenocarcinoma
R F BOHNEN, M BANISADRE, R N GULBRANDSON, and E D ZANJANI

418 Prenatal Diagnosis of Noonan's Syndrome in a Female Infant With Spontaneous Resolution of Cystic Hygroma and Hydrops
L IZQUIERDO, O KUSHNIR, D SANCHEZ, L CURET, P OLNEY, G E SARTO, C CLERICUZIO, and R OLNEY

421 Chylothorax and Respiratory Failure in Kaposi's Sarcoma
D W PENNINGTON, M L WARNOCK, and M S STULBARG

423 Fatal Pulmonary Infection With *Mycobacterium fortuitum*
J M NUSSBAUM and P N R HESELTINE

**CORRESPONDENCE**

426 Asthma Deaths • Thymic Carcinoid and Multiple Endocrine Neoplasia • Iatrogenic Illness • The War on Drugs • The Eye of the Beholder • Tryptophan Use and Fasciitis • Integration of Prevention Efforts • Life-style and Illness

**TOPICS IN PRIMARY CARE MEDICINE**

430 Dupuytren's Disease
S M GONZALEZ and R I GONZALEZ

**HEALTH CARE DELIVERY**

434 Health Care Needs and Services for Technology-Dependent Children in Developmental Centers
L S CRAIN, D N MANGRAVITE, R ALLPORT, M SCHOUR, and K BIAKANJA

**RADIOLOGIC CASE**

439 A 36-Year-Old Woman With a Pulsatile Mass of the Left Tympanic Membrane
J REISER, K S DANIELSON, J M LEVY, R D ZONIS, and F K CHRISTENSEN

**IN THE FOREFRONT**

441 Developing Principles for Prudent Health Care Allocation—The Continuing Oregon Experiment
R CRAWSHAW, M GARLAND, B HINES, and B ANDERSON

**MEDICAL ETHICS**

447 A Policy Concerning the Therapeutic Use of Human Fetal Tissue in Transplantation
R M NELSON

**LESSONS FROM THE PRACTICE**

449 The Trivia Champ and Honorary Faculty Member
W B SHORE

**OTHER FEATURES**

354 Subscription Information

362 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

450 Book Reviews

451 Information for Authors

453 Classified Advertising

464 Western State Medical Associations' Meetings

**Detailed Table of Contents:** 352, 356, 359


Official Journal of the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology

# THERAPY THAT MAY BE AS SILENT AS HYPERTENSION ITSELF

VASOTEC® (Enalapril Maleate, MSD) is generally well tolerated and not characterized by certain undesirable effects associated with selected agents in other antihypertensive classes.

VASOTEC is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

A diminished antihypertensive effect toward the end of the dosing interval can occur in some patients.

For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

Copyright © 1989 by Merck & Co., Inc.

FOR MANY HYPERTENSIVE PATIENTS
ONCE-A-DAY
VASOTEC®
(ENALAPRIL MALEATE | MSD)

# VASOTEC®

## (ENALAPRIL MALEATE | MSD)

VASOTEC is available in 2.5-mg, 5-mg, 10-mg, and 20-mg tablet strengths.

**Contraindications:** VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor

**Warnings:** *Angioedema* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms Angioedema associated with laryngeal edema may be fatal **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS )

*Hypotension* Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone Patients with heart failure given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed, caution should be observed when initiating therapy (See DOSAGE AND ADMINISTRATION ) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary

*Neutropenia/Agranulocytosis:* Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered

**Precautions:** *General Impaired Renal Function.* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy In such patients, renal function should be monitored during the first few weeks of therapy

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required

**Evaluation of patients with hypertension or heart failure should always include assessment of renal function.** (See DOSAGE AND ADMINISTRATION )

*Hyperkalemia* Elevated serum potassium (>5 7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials In most cases these were isolated values which resolved despite continued therapy Hyperkalemia was a cause of discontinuation of therapy in 0 28% of hypertensive patients In clinical trials in heart failure, hyperkalemia was observed in 3 8% of patients, but was not a cause for discontinuation

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC (See *Drug Interactions* )

*Surgery/Anesthesia* In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion

*Information for Patients:*

*Angioedema* Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician

*Hypotension* Patients should be cautioned to report lightheadedness, especially during the first few days of therapy If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure, patients should be advised to consult with the physician.

*Hyperkalemia* Patients should be told not to use salt substitutes containing potassium without consulting their physician.

*Neutropenia* Patients should be told to report promptly any indication of infection (e g , sore throat, fever) which may be a sign of neutropenia

NOTE As with many other drugs, certain advice to patients being treated with enalapril is warranted This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects

*Drug Interactions*

*Hypotension: Patients on Diuretic Therapy* Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

*Agents Causing Renin Release:* The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e g , diuretics)

*Other Cardiovascular Agents:* VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions

*Agents Increasing Serum Potassium* VASOTEC attenuates potassium loss caused by thiazide-type diuretics Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC

*Lithium.* Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

*Pregnancy – Category C:* There was no teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline Enalapril was not teratogenic in rabbits However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters

There are no adequate and well-controlled studies of enalapril in pregnant women However, data are available that show enalapril crosses the human placenta Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined, VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity

*Nursing Mothers* Milk in lactating rats contains radioactivity following administration of $^{14}C$ enalapril maleate It is not known whether this drug is secreted in human milk Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

*Pediatric Use* Safety and effectiveness in children have not been established

**Adverse Reactions:** VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients

*HYPERTENSION* The most frequent clinical adverse experiences in controlled trials were headache (5.2%), dizziness (4 3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1 4%), nausea (1 4%), rash (1 4%), cough (1.3%), orthostatic effects (1 2%), and asthenia (1.1%).

*HEART FAILURE* The most frequent clinical adverse experiences in both controlled and uncontrolled trials were dizziness (7 9%), hypotension (6.7%), orthostatic effects (2 2%), syncope (2 2%), cough (2.2%), chest pain (2 1%), and diarrhea (2.1%)

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1 5%), nausea (1 3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1 3%), and myocardial infarction (1.2%)

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0 5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category

*Cardiovascular* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction, pulmonary edema, rhythm disturbances, atrial fibrillation, palpitation.

*Digestive:* Ileus, pancreatitis, hepatitis (hepatocellular or cholestatic jaundice), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth

*Musculoskeletal:* Muscle cramps

*Nervous/Psychiatric.* Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

*Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

*Respiratory* Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection.

*Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, hyperhidrosis

*Special Senses* Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgias/arthritis, myalgias, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash, and other dermatologic manifestations.

*Angioedema.* Angioedema has been reported in patients receiving VASOTEC (0 2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately (See WARNINGS )

*Hypotension* In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0 5% of patients following the initial dose or during extended therapy Hypotension or syncope was a cause for discontinuation of therapy in 0 1% of hypertensive patients In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2 2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure (See WARNINGS.)

*Clinical Laboratory Test Findings:*

*Serum Electrolytes:* Hyperkalemia (see PRECAUTIONS), hyponatremia

*Creatinine, Blood Urea Nitrogen* In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0 2% of patients with essential hypertension treated with VASOTEC alone Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis (See PRECAUTIONS ) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1 2% of patients.

*Hemoglobin and Hematocrit* Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0 3 g% and 1.0 vol%, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0 1% of patients discontinued therapy due to anemia

*Other (Causal Relationship Unknown)* In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported. A few cases of hemolysis have been reported in patients with G6PD deficiency

*Liver Function Tests.* Elevations of liver enzymes and/or serum bilirubin have occurred

**Dosage and Administration:** *Hypertension* In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS ) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (See WARNINGS and PRECAUTIONS, *Drug Interactions.*)

The recommended initial dose in patients not on diuretics is 5 mg once a day Dosage should be adjusted according to blood pressure response The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS)

*Dosage Adjustment in Hypertensive Patients with Renal Impairment.* The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

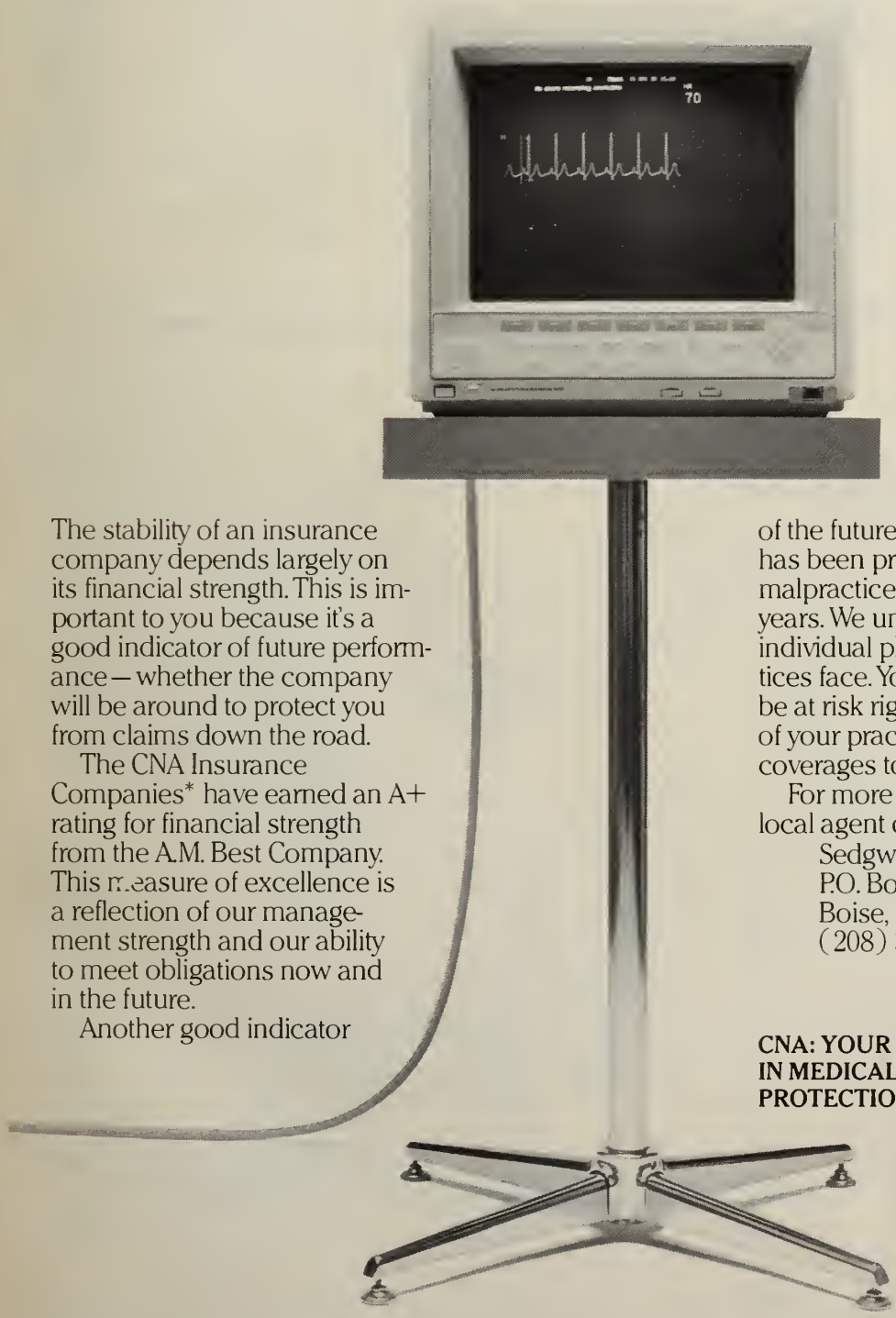
*Heart Failure:* VASOTEC is indicated as adjunctive therapy with diuretics and digitalis The recommended starting dose is 2.5 mg once or twice daily After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects.*) Dosage may be adjusted depending upon clinical or hemodynamic response (See WARNINGS.)

*Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia:* In patients with heart failure who have hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine >1 6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, *Heart Failure,* WARNINGS, and PRECAUTIONS, *Drug Interactions.*) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg

*For more detailed information, consult your MSD Representative or see Prescribing Information, Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.* J9VS54R3(819)

MSD
MERCK SHARP & DOHME

# CNA's financial stability can be vital to the health of your practice.



The stability of an insurance company depends largely on its financial strength. This is important to you because it's a good indicator of future performance—whether the company will be around to protect you from claims down the road.

The CNA Insurance Companies* have earned an A+ rating for financial strength from the A.M. Best Company. This measure of excellence is a reflection of our management strength and our ability to meet obligations now and in the future.

Another good indicator of the future is past performance. CNA has been protecting doctors against malpractice claims for more than 20 years. We understand the special risks individual physicians and group practices face. Your personal assets could be at risk right along with the assets of your practice, and we can tailor coverages to meet your exact needs.

For more information, contact your local agent or:

Sedgwick James of Idaho, Inc.
P.O. Box 8688
Boise, ID 83707
(208) 342-6573

**CNA: YOUR PARTNER IN MEDICAL MALPRACTICE PROTECTION**

*The CNA Physicians Protection Program is underwritten by Continental Casualty Company, one of the CNA Insurance Companies.

**CNA**
**For All the Commitments You Make®**

## *The Western Journal of Medicine*

(ISSN 0093-0415/USPS 084 480) is published monthly for $30 per year (USA and Canada) by the California Medical Association, 221 Main Street, San Francisco, CA 94105. Second-class postage paid at San Francisco, CA and additional mailing offices.

**POSTMASTER:**
Send address changes to
*The Western Journal of Medicine*
Circulation, P.O. Box 7602
San Francisco, CA 94120-7602


# *Moving?*

Please give us six weeks notice and supply your personal reference number.

**ID No.**

**302703 XX**

SAMPLE

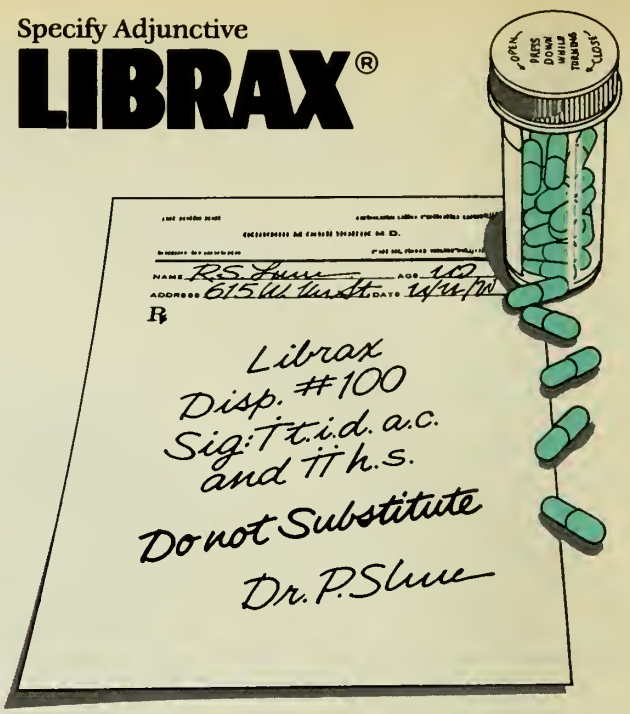
**The Western Journal of Medicine**
**P.O. Box 7602**
**San Francisco, CA 94120-7602**

**The Western Journal of Medicine**

**P.O. Box 7602**
**San Francisco, CA 94120-7602**


Specify Adjunctive

# LIBRAX®




**Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.**

**Please consult complete prescribing information, a summary of which follows:**

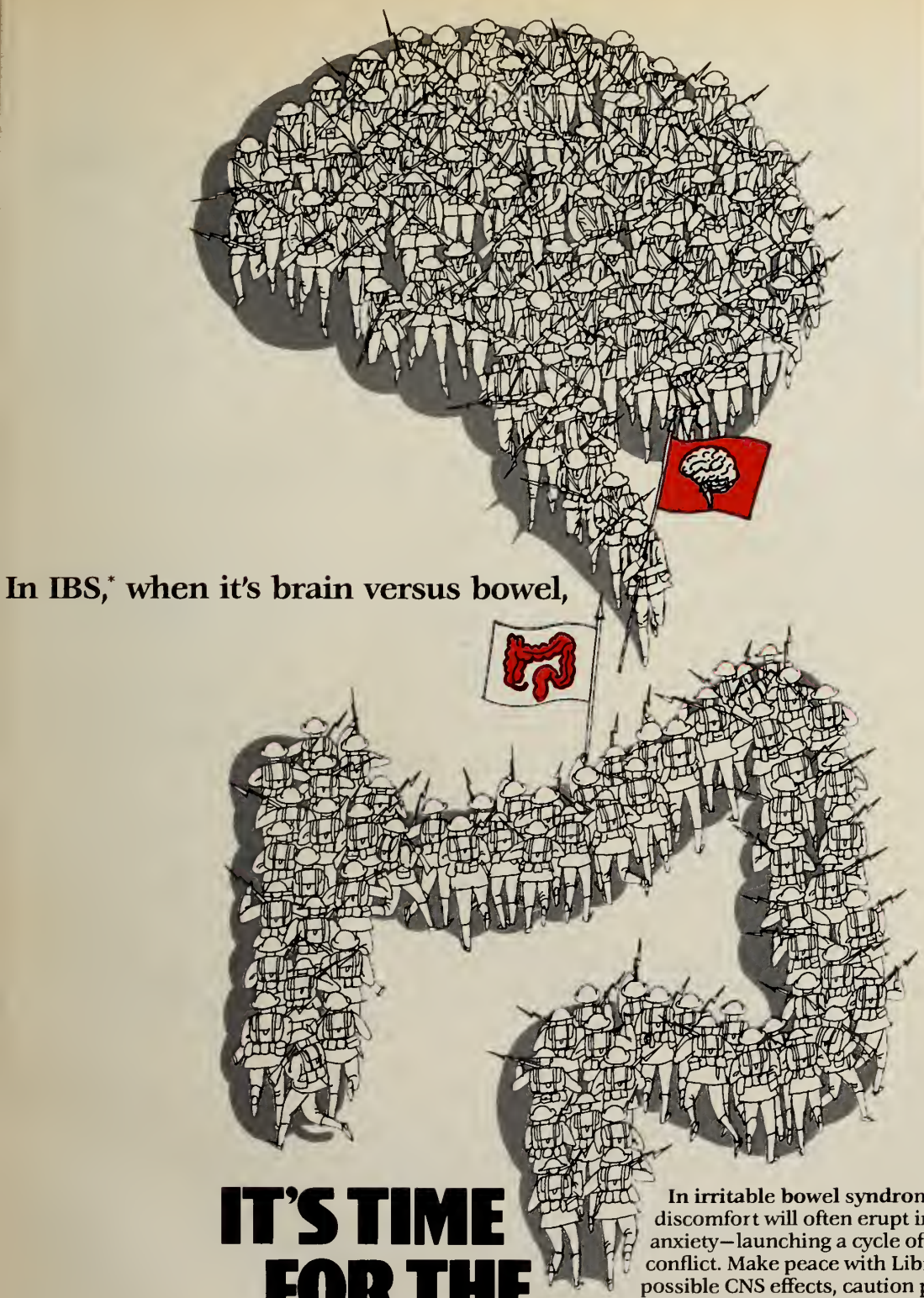
* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

**Contraindications:** Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
**Warnings:** Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
*Usage in Pregnancy:* **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
**Precautions:** In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
**Adverse Reactions:** No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
**Drug Abuse and Dependence:** Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

P.I. 0288

ROCHE® **Roche Products**

Roche Products Inc.
Manati, Puerto Rico 00701




Be sure to specify Librax, "Do not Substitute" or your state's equivalent statement on your prescription.

# IT'S TIME FOR THE PEACEMAKER.

**In irritable bowel syndrome,*** intestinal discomfort will often erupt in tandem with anxiety—launching a cycle of brain/bowel conflict. Make peace with Librax. Because of possible CNS effects, caution patients about activities requiring complete mental alertness.

*Librax has been evaluated as possibly effective as adjunctive therapy in the treatment of peptic ulcer and IBS.

Specify Adjunctive

**LIBRAX®**

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

ROCHE®

Copyright © 1989 by Roche Products Inc. All rights reserved.

Please see summary of prescribing information on adjacent page.

# The Western Journal of Medicine

SINCE 1902 ISSN 0093-0415

PO BOX 7602 • SAN FRANCISCO, CALIFORNIA 94120-7602 • TELEPHONE (415) 541-0900



LINDA HAWES CLEVER, MD, *Editor*
LLOYD H. SMITH, Jr, MD, *Associate Editor*
DIANA L. McANINCH, *Managing Editor*
SALLY LINEBARGER, *Assistant Managing Editor*
SANDRA WILLETT, *Editorial Assistant*
JANICE ANDERSEN, *Senior Copy Editor*
FRITZ C. HEATON, *Advertising and Promotion Manager*
NILA J. NICHOLS, *Circulation Coordinator*
DOROTHY A. HEARST, *Classified Advertising*

editorial communications to DR CLEVER • business communications to MS McANINCH



Official Journal of the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.



## EDITORIAL BOARD

*Editor Emeritus*
Malcolm S. M. Watts, San Francisco, Calif

*Editor Emeritus*
Dwight L. Wilbur, San Francisco, Calif

*Editor for Clinical Investigation*
Kenneth D. Gardner, Jr, Albuquerque, NM

*Special Editor for Arizona*
Marshall B. Block, Phoenix, Ariz

*Special Editor for Denver*
David Shander, Denver, Colo

*Special Editor for Idaho*
E. R. W. Fox, Coeur d'Alene, Idaho

*Special Editor for Nevada*
Anton P. Sohn, Reno, Nev

*Special Editor for New Mexico*
I. Brian Taylor, Carlsbad, NM

*Special Editor for Utah*
John H. Holbrook, Salt Lake City, Utah

*Special Editor for Washington*
David Hopkins, Federal Way, Wash

*Special Editor for Wyoming*
Joseph P. Murphy, Casper, Wyo

*Allergy*
Merle S. Scherr, Scottsdale, Ariz

*Anesthesiology*
Ronald D. Miller, San Francisco, Calif

*Biostatistics and Epidemiology*
Virginia L. Ernster, San Francisco, Calif

*Cardiac and Thoracic Surgery*
Norman E. Shumway, Stanford, Calif

*Chest Diseases*
Leonard D. Hudson, Seattle, Wash
Thomas L. Petty, Denver, Colo

*Dermatology*
Clark Huff, Denver, Colo
Frank Parker, Portland, Ore
Gerald D. Weinstein, Irvine, Calif

*Emergency Medicine*
William A. Boehm, Alamogordo, NM
W. Richard Bukata, Flintridge, Calif
Clark Chipman, Portland, Ore
Thomas Elmendorf, Davis, Calif

*General and Family Practice*
Charles W. Huff, Casper, Wyo
Norman Kahn, Sacramento, Calif
J. Jerome Wildgen, Kalispell, Mont

*Internal Medicine*
Philip R. Alper, Burlingame, Calif
Robert W. Burroughs, Spokane, Wash
Patricia Gabow, Denver, Colo
Harry R. Kimball, Boston, Mass
Darwin Palmer, Albuquerque, NM
George A. Porter, Portland, Ore
Irwin J. Schatz, Honolulu, Hawaii
Stephen I. Wasserman, San Diego, Calif
Laurens P. White, San Francisco, Calif

*Neurology*
J. Richard Baringer, Salt Lake City, Utah
Don F. Seelinger, Albuquerque, NM
W. C. Wiederholt, La Jolla, Calif

*Neurosurgery*
George A. Djemann, Seattle, Wash
Robert F. Spetzler, Phoenix, Ariz
Charles B. Wilson, San Francisco, Calif

*Nuclear Medicine*
Philip Matin, Roseville, Calif

*Obstetrics and Gynecology*
Daniel Mishell, Jr, Los Angeles, Calif
Morton A. Stenchever, Seattle, Wash

*Occupational Medicine*
Linda Rosenstock, Seattle, Wash

*Ophthalmology*
John L. Keltner, Davis, Calif
Bruce E. Spivey, San Francisco, Calif

*Orthopedics*
George E. Dmer, Albuquerque, NM

*Otolaryngology*
Paul H. Ward, Los Angeles, Calif

*Pathology*
Roy I. Davis, Phoenix, Ariz

*Pediatrics*
Roberta A. Ballard, San Francisco, Calif
Allen W. Mathies, Jr, Pasadena, Calif
William D. Robertson, Seattle, Wash

*Pharmacology*
Rubin Bressler, Tucson, Ariz

*Physical Medicine and Rehabilitation*
Julie G. Madorsky, Pomona, Calif

*Plastic Surgery*
Richard P. Jobe, Los Altos, Calif
Henry K. Kawamoto, Jr, Santa Monica, Calif

*Preventive Medicine and Public Health*
Joseph L. Lyon, Salt Lake City, Utah
Jonathan Mann, Geneva, Switz

*Psychiatry*
Ralph Crawshaw, Portland, Ore
Alan I. Levenson, Tucson, Ariz
R. Bruce Sloane, Los Angeles, Calif

*Radiology*
Gary Glazer, Stanford, Calif
Michael L. Manco-Johnson, Denver, Colo
Albert A. Moss, Seattle, Wash

*Surgery*
Haile T. Debas, San Francisco, Calif
Alex G. Little, Las Vegas, Nev
Frank G. Moody, Houston, Tex

*Urology*
Paul H. Lange, Seattle, Wash

*Senior Member at Large*
Edgar Wayburn, San Francisco, Calif

## ADVISORY BOARD, CLINICAL INVESTIGATION

George D. Molnar, Univ of Alberta
Murray A. Katz, Univ of Arizona
Ross E. Petty, Univ of British Columbia
Eldon Shaffer, Univ of Calgary
M. Eric Gershwin, Univ of California, Davis
Jacob Katz, Univ of California, Irvine
Delbert A. Fisher, Univ of California, Los Angeles
Kenneth M. Moser, Univ of California, San Diego
H. Benfer Kaltreider, Univ of California, San Francisco
Alan S. Nies, Univ of Colorado
Irwin J. Schatz, Univ of Hawaii
John Peacock, Univ of Nevada
Sanford Schneider, Loma Linda Univ
Kenneth D. Gardner, Jr, Univ of New Mexico
J. David Bristow, Univ of Oregon
Robert M. McAllister, Univ of Southern California
R. Marvin Bala, Univ of Saskatchewan
Allen D. Cooper, Stanford Univ
Gerald Rothstein, Univ of Utah
David R. Saunders, Univ of Washington



## ADVERTISING INFORMATION

Advertising Sales Representatives

EAST/MIDWEST: Cunningham Associates, James C. Cunningham and James Pattis, PO Box 308, Park Ridge, NJ 07656 • (201) 767-4170/FAX (201) 767-8065

WEST: Lynne Jeffes, 10 Acacia Lane, Redwood City, CA 94062 • (415) 368-1898

CLASSIFIED: PO Box 7602, San Francisco, CA 94120-7602; overnight mail, 221 Main St, San Francisco, CA 94105 • Tel: (415) 541-0900, ext. 376

*Advertisements*—The journal is published the first week of the month. Advertising copy must be received no later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee. *The journal reserves the right to reject any advertisement.*


## SUBSCRIPTION INFORMATION

The subscription price per year is $30 in the United States and Canada (US funds); $50 in all other countries. Single copies are $5.00. USA/CANADA postage and handling included. All other countries add US $4 23 Air Printed Matter Postage. Address all subscription communications to:

THE WESTERN JOURNAL OF MEDICINE Circulation, PO Box 7602
San Francisco, CA 94120-7602 • Tel: (415) 882-5179

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $5.00 is applicable for each issue available.

*Change of Address*—Requests for change of address should give both the old and new address. Allow six weeks for changeover.

## SUBMITTING MANUSCRIPTS

Manuscripts for consideration should be sent to the editor, Linda Hawes Clever, MD, PO Box 7602, San Francisco, CA 94120-7602; overnight mail, 221 Main St, San Francisco, CA 94105.

*"Information for Authors"*—A complete guide to manuscript submission and *WJM* style appears in the January and July issues. Manuscripts may be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (*Annals of Internal Medicine*, Feb 1988; *The Medical Journal of Australia*, Feb 1988).

*Author Responsibility*—Authors are responsible for all statements, conclusions and methods of presenting subjects. Articles are accepted on condition that they are contributed solely to this journal.

*Manuscripts*—Ordinarily manuscripts should not exceed 3,000 words (less than 15 typed double-spaced pages). The *original* manuscript and two copies should be submitted, typed double-spaced throughout. If photographic illustrations are desired, three sets of clear, unmounted black and white glossy prints should be supplied. For line drawings, original artwork or glossy prints are acceptable. Tables should be typed on separate sheets of paper.

*Clinical Investigation*—Papers that authors wish considered for the Clinical Investigation section should be so designated in the transmittal letter. Such papers should describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease.

## PUBLISHER


Copyright 1990 by the California Medical Association • Owned and Published by the California Medical Association.

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with January and July.



***The Western Journal of Medicine***

(ISSN 0093-0415/USPS 084 480) is published monthly for $30 per year (USA and Canada) by the California Medical Association, 221 Main Street, San Francisco, CA 94105. Second-class postage paid at San Francisco and additional mailing offices.

**POSTMASTER:** Send address changes to *The Western Journal of Medicine*, Circulation, PO Box 7602, San Francisco, CA 94120-7602.

# TAKE A CLOSER LOOK

*at MGMA's Professional Liability Program...it may just expand your group's coverage and lower your cost.*

- Combined purchasing power of participating MGMA member groups.
- A.M. Best A+ (Superior) rated carriers.
- Exclusive to qualified MGMA member groups.
- Prior Acts coverage.
- Flexible limits of liability.
- Retrospective dividends.
- No cost reporting endorsement for disability or death.
- No cost reporting endorsement after 5 years and age 55.
- Other exclusive reporting endorsement benefits.

For more than 20 years, thousands of MGMA member groups have been provided with sound employee benefit insurance plans through The MGIS Companies. Now may be a good time for you to find out more about medical-professional liability plans offered exclusively to MGMA member groups.

Dividends are not guaranteed. Not all features available in all States.

the mgis companies

*National Program Manager:*

**MGIS Property & Casualty Insurance Services, Inc.**

85 Great Oaks Boulevard, San Jose, CA 95119
Post Office Box 23400, San Jose, CA 95153-5351
408-365-3799 Toll Free: 800-969-MGIS Fax: 408-226-0271

# Investigators' evaluations confirm hair growth in male pattern baldness of the vertex

ROGAINE® Topical Solution (minoxidil 2%) is the *first* prescription medication proved effective for male pattern baldness of the vertex. The effect on frontal baldness has not been adequately studied.

Evidence of growth was demonstrated by physician evaluations of 1,431 patients in 27 centers across the United States. Patients were placed on ROGAINE or placebo and evaluated each month for four months. Response was judged to be no growth, new vellus (baby) hair, or minimal, moderate, or dense growth.

In addition, after the placebo group was discontinued, continuous application of ROGAINE over an additional eight months was evaluated to determine if nonvellus growth could be sustained.

START OF STUDY

START OF STUDY

START OF STUDY

Examples of minimal, moderate, and dense growth as evaluated by investigators

© 1989 The Upjohn Company

MINIMAL GROWTH

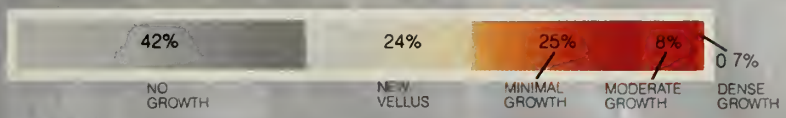
MODERATE GROWTH

DENSE GROWTH

*Four-Month Phase*

At the end of four months, 34% of 714 patients treated with ROGAINE were evaluated as showing minimal, moderate, or dense growth, while 20% of 717 patients showed minimal, moderate, or dense growth with placebo, a highly significant difference ($P<.0005$).

**Rogaine** (714)




**Placebo** (717)

*Non-Placebo-Controlled Continuation Phase*

After 12 months, dense growth was observed in 8% of the 619 patients treated with ROGAINE, moderate growth in 31%, and minimal growth in 37%. Approximately one fourth of patients showed only vellus hair growth or no growth.

**Rogaine** (619)

*Compliance is Essential*

The multicenter studies indicate that a period of *four months or longer* of daily b.i.d. applications of ROGAINE is usually necessary before evidence of hair growth is apparent. Hair growth continued to increase in study subjects over months 5 through 12.

Continuous use is necessary to maintain hair growth. Newly grown hair returns to the untreated state three to four months after cessation of therapy with ROGAINE.

*Please see last page for brief summary of prescribing information.*

**Rogaine®** Rx

TOPICAL SOLUTION minoxidil 2%

**Upjohn**

The Upjohn Company
Kalamazoo, MI 49001 USA

# Rogaine® Rx

TOPICAL SOLUTION minoxidil 2%

**INDICATIONS AND USAGE**
Male pattern baldness (alopecia androgenetica) of the vertex of the scalp No effect has been seen on frontal baldness At least four months of treatment are generally required before evidence of hair growth can be expected, further growth continues through one year The new growth is not permanent, cessation of treatment will lead to its loss in a few months

**CONTRAINDICATIONS**
Hypersensitivity to minoxidil, propylene glycol or ethanol

**WARNINGS**
*1 Need for normal scalp* Before starting treatment, make sure that the patient has a normal, healthy scalp Local abrasion or dermatitis may increase absorption and hence the risk of side effects
*2. Potential adverse effects* Although extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects, greater absorption due to misuse, individual variability or unusual sensitivity could, at least theoretically, produce a systemic effect
Experience with oral minoxidil has shown the following major cardiovascular effects (Review the package insert for LONITEN® Tablets for details):
—salt and water retention, generalized and local edema
—pericardial effusion, pericarditis, tamponade
—tachycardia
—increased incidence of angina or new onset of angina
Patients with underlying heart disease, including coronary artery disease and congestive heart failure, would be at particular risk of these potential effects Additive effects could also emerge in patients being treated for hypertension
Potential patients should have a history and physical, should be advised of potential risks and a risk/benefit decision should be made Heart patients should realize that adverse effects may be especially serious Alert patients to the possibility of tachycardia and fluid retention, and monitor for increased heart rate, weight gain or other systemic effects

**PRECAUTIONS**
*General Precautions* Monitor patients one month after starting ROGAINE and at least every six months afterward Discontinue ROGAINE if systemic effects occur. The alcohol base will burn and irritate the eye If ROGAINE reaches sensitive surfaces (eg, eye, abraded skin and mucous membranes) bathe with copious cool water
Avoid inhaling the spray
Do not use in conjunction with other topical agents such as corticosteroids, retinoids and petrolatum or agents that enhance percutaneous absorption ROGAINE is for topical use only Each mL contains 20 mg minoxidil and accidental ingestion could cause adverse systemic effects
Decreased integrity of the epidermal barrier caused by inflammation or disease of the skin, eg, excoriations, psoriasis or severe sunburn, may increase minoxidil absorption.
*Patient Information:* A patient information leaflet is included with each package and in the full product information
*Drug Interactions* No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine.
*Carcinogenesis, Mutagenesis and Impairment of Fertility* No carcinogenicity was found with topical application. Oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice In rats, there was a dose-dependent reduction in conception rate.
*Pregnancy Category C:* ROGAINE should not be used by pregnant women
*Labor and Delivery* The effects are not known.
*Nursing Mothers* ROGAINE should not be administered
*Pediatric Use.* Safety and effectiveness have not been established under age 18

**ADVERSE REACTIONS**
ROGAINE was used by 3510 patients in placebo-controlled trials Except for dermatologic events, no individual reaction or reactions grouped by body systems appeared to be increased in the minoxidil-treated patients
**Respiratory** (bronchitis, upper respiratory infection, sinusitis) 5 95%, **Dermatologic** (irritant or allergic contact dermatitis) 5 27%, **Gastrointestinal** (diarrhea, nausea, vomiting) 3 42%; **Neurology** (headache, dizziness, faintness, light-headedness) 2 56%, **Musculoskeletal** (fractures, back pain, tendinitis) 2 17%, **Cardiovascular** (edema, chest pain, blood pressure increases/decreases, palpitation, pulse rate increases/decreases) 1 28%, **Allergy** (non-specific allergic reactions, hives, allergic rhinitis, facial swelling and sensitivity) 1 03%, **Special Senses** (conjunctivitis, ear infections, vertigo) 0 94%, **Metabolic-Nutritional** (edema, weight gain) 0 60%, **Urinary Tract** (urinary tract infections, renal calculi, urethritis) 0 46%, **Genital Tract** (prostatitis, epididymitis) 0 46%, **Psychiatric** (anxiety, depression, fatigue) 0 28%, **Hematology** (lymphadenopathy, thrombocytopenia) 0 23%, **Endocrine** 0 09%
Patients have been followed for up to 5 years and there has been no change in incidence or severity of reported reactions. Additional events reported since marketing include: eczema, hypertrichosis, local erythema, pruritus, dry skin/scalp flaking, sexual dysfunction, visual disturbances including decreased visual acuity, exacerbation of hair loss, alopecia

**DOSAGE AND ADMINISTRATION**
Hair and scalp should be dry before application. 1 mL should be applied to the total affected areas twice daily Total daily dose should not exceed 2 mL. If the fingertips are used to facilitate drug application, wash the hands afterwards

**HOW SUPPLIED**
60 mL bottle with multiple applicators NDC 0009-3367-05
Caution: Federal law prohibits dispensing without a prescription.

B-1-S

**Upjohn**

The Upjohn Company
Kalamazoo, MI 49001 USA

© 1989 The Upjohn Company June 1989 J-9909



# YOCON®
## YOHIMBINE HCl

**Description:** Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

**Action:** Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it, however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

**Indications:** Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

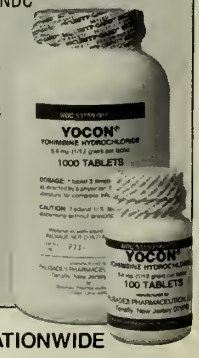
**Contraindications:** Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

**Warning:** Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

**Adverse Reactions:** Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

**Dosage and Administration:** Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

**How Supplied:** Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.




**References:**
1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

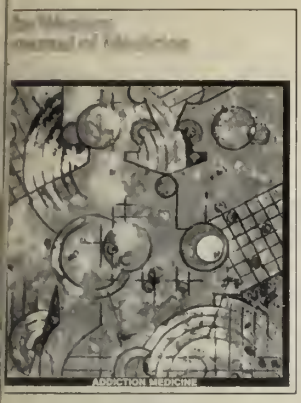
Rev. 1/85

**AVAILABLE AT PHARMACIES NATIONWIDE**

**PALISADES PHARMACEUTICALS, INC.**
219 County Road
Tenafly, New Jersey 07670
**(201) 569-8502**
**1-800-237-9083**

# SPECIAL ISSUES

THE WESTERN JOURNAL OF MEDICINE Special May Issue:

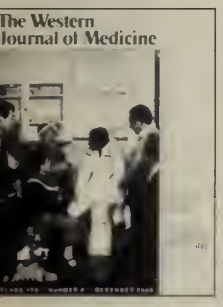


MAY 1990

## Addiction Medicine
### and the Primary Care Physician

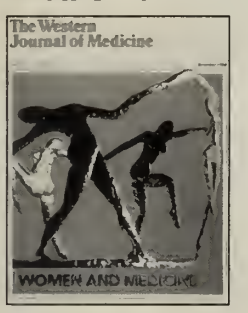
- OVERVIEW OF ADDICTION MEDICINE *David Smith, Editor/Founder, Haight-Ashbury Free Clinic*
- CHEMICAL DEPENDENCE AND THE WORK PLACE *John Osterloh and Charles Becker*
- THE DISEASE CONCEPT OF ALCOHOLISM *John Wallace*
- COGNITIVE IMPAIRMENTS IN RECOVERING ALCOHOLICS *George Fein*
- SUBSTANCE ABUSE AND PULMONARY PATHOLOGY *Donald Tashkin*
- SPECIAL POPULATIONS: THE ADOLESCENT *Martha Morrison*
- METHADONE MAINTENANCE IN THE TREATMENT OF OPIOID DEPENDENCE *Joan Zweben*
- TREATMENT OF NICOTINE DEPENDENCE IN THE CHEMICALLY DEPENDENT PATIENT *Karen Sees*
- PHARMACOLOGIC APPROACHES TO THE TREATMENT OF COCAINE DEPENDENCE *Wanda A. Taylor and Mark S. Gold*

## Cross-cultural Medicine



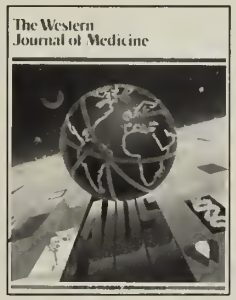

Cross-cultural medicine is devoted to the care of patients of different, cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983. 2nd reprinted edition.

## Women and Medicine



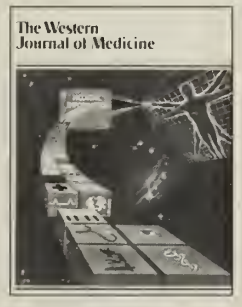

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients. Topics covered include liver disease, women and AIDS, heart disease, hysterectomy, PMS, ovarian cancer, and women physicians and organized medicine. Linda Hawes Clever, MD, Special Issue Editor, 1988.

## AIDS— A Global Perspective



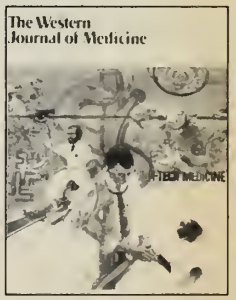

This issue, from the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent. Jonathan M. Mann, MD, Special Issue Editor, 1987.

## Medical Informatics




*Medical Informatics* explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

## High-Tech Medicine




This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

---

| Quantity | Per Copy* |
|---|---|
| Single copy | $5.00 |
| 2 to 10 | 4.00 |
| 11 to 50 | 3.50 |
| More than 50 | 3.00 |
| Cross-cultural | 7.50 |
| 50 copies or more | 6.50 |

**Note:** USA/Canada postage and handling included, all other countries please add US $4.23 Air Printed Matter postage. Please add California and local sales tax where applicable.

## ORDER FORM

WJM 4/90

Name _____

Address _____ City/State/Zip _____

Charge my account: ☐ VISA ☐ MASTERCARD

# _____ Exp. date _____

Signature _____

Mail to: Circulation Department, The Western Journal of Medicine
P.O. Box 7602, San Francisco, CA 94120-7602

**Please send me:**

____copies of Addiction Medicine and the Primary Care Physician

____copies of Cross-cultural Medicine

____copies of Women and Medicine

____copies of AIDS—A Global Perspective

____copies of High-Tech Medicine

____copies of Medical Informatics

Payment must accompany order. Total amount enclosed $

The Western Journal of Medicine

VOLUME 152 • NUMBER 4 • APRIL 1990

# CONTENTS

## CLINICAL MEDICINE

377 **Physical Diagnosis Versus Modern Technology—A Review**
FAITH T. FITZGERALD, MD
*From the Department of Internal Medicine, University of California, Davis, Medical Center, Sacramento.*

383 **Current Management of the Wolff-Parkinson-White Syndrome**
ANDREW ARAI, MD, and JACK KRON, MD
*From the Division of Cardiology, Department of Medicine, Oregon Health Sciences University School of Medicine, Portland.*

## MEDICAL PROGRESS

392 **Perspective on Hypertension in the Elderly**
BARBARA WHITCOMB, MD, and RICHARD L. BYYNY, MD
*From the Division of Internal Medicine, University of Colorado Health Sciences Center, Denver.*

## MEDICAL STAFF CONFERENCE

401 **Immunotherapy for Infectious Diseases**
Discussant: JAMES E. PENNINGTON, MD
*A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco, School of Medicine. Taken from a transcription, it was prepared by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.*

## EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

**Obstetrics and Gynecology**
*Items of progress in obstetrics and gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance.*

406 **Avoiding Pregnancy in Isotretinoin Users**
RON E. SWENSEN, MD

406 **An Ovarian Cancer Tumor Marker, CA 125, Comes of Age**
RICHARD E. BULLER, MD, PhD, and PHILIP J. DiSAIA, MD

407 **Drug Therapy for Genital Herpes**
PAUL A. HENSLEIGH, MD, PhD

407 **$\beta$-Streptococcal Cultures in Obstetrics**
R. HAROLD HOLBROOK, MD

408 **Estrogen Hormone Replacement to Minimize Cardiovascular Risk**
L. MICHAEL KETTEL, MD

409 **Gonadotropin-Releasing Hormone Agonist Treatment of Endometriosis and Myomas**
LINDA C. GIUDICE, MD, PhD

409 **Endometrial Ablation**
ARNOLD KRESCH, MD

410 **Medical Treatment of Ectopic Pregnancy**
AMIN A. MILKI, MD, and JAMSHID MOOSSAZADEH, MD

410 **New Therapies for Genital Warts**
DAVID A. GRIMES, MD

411 **Laparoscopic Surgery for Ectopic Pregnancy**
G. DAVID ADAMSON, MD

*(Continued on Page 356)*

Her anxiolytic is working—but she's alert, functioning, and at no risk of a benzodiazepine withdrawal syndrome when therapy ends.

## BuSpar relieves anxiety and returns your patient to normal activity

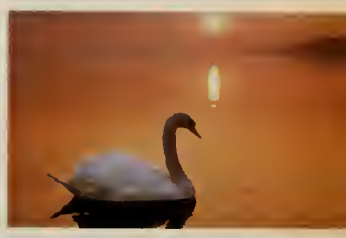
...with no more sedation (10%) than induced by placebo (9%)[1]
...without inducing significant cognitive[2] or functional impairment*
...without producing a benzodiazepine withdrawal syndrome[3] upon discontinuation

*Effective choice for anxiety*

# BuSpar®

Tablets, 5 mg and 10 mg

(buspirone HCl)



*for a different kind of calm*

*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

For Brief Summary, please see following page.

© 1989, Bristol-Myers Company, Evansville, Indiana 47721, U.S.A.

MJL8-4270

# BuSpar® (buspirone HCl)

**References:** 1. Newton RE *et al* A review of the side effect profile of buspirone *Am J Med* 1986,80(3B) 17-21 2. Lucki I, *et al* Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function *Br J Clin Pharmacol* 1987,23 207-211 3. Lader M Assessing the potential for buspirone dependence or abuse and effects of its withdrawal *Am J Med* 1987,82(5A) 20-26

**Contraindications:** Hypersensitivity to buspirone hydrochloride
**Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard.** Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment
**Precautions:** ***General***—*Interference with cognitive and motor performance.* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.
*Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients:* Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.
*Possible concerns related to buspirone's binding to dopamine receptors:* Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia) Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity, however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).
***Information for Patients***—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone, to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone, to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.
***Drug Interactions***—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**) Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.
***Carcinogenesis, Mutagenesis, Impairment of Fertility***—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur
***Pregnancy: Teratogenic Effects***—Pregnancy Category B Should be used during pregnancy only if clearly needed.
***Nursing Mothers***—Administration to nursing women should be avoided if clinically possible
***Pediatric Use***—The safety and effectiveness have not been determined in individuals below 18 years of age
***Use in the Elderly***—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.
***Use in Patients with Impaired Hepatic or Renal Function***—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.
**Adverse Reactions (See also Precautions):** ***Commonly Observed***—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement
***Associated with Discontinuation of Treatment***—The more common events causing discontinuation included: central nervous system disturbances (3 4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1 1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary
***Incidence in Controlled Clinical Trials***—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials. *Cardiovascular:* Tachycardia/palpitations 1% *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2% *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1% *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1% *Skin:* Skin rash 1% *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%
***Other Events Observed During the Entire Premarketing Evaluation***—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients, and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding, rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise, rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.
***Postintroduction Clinical Experience***—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined
**Drug Abuse and Dependence:** ***Controlled Substance Class***—Not a controlled substance
***Physical and Psychological Dependence***—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).
**Overdosage:** ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.
***Recommended Overdose Treatment***—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined
*For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.*
U.S. Patent Nos. 3,717,634 and 4,182,763
MJL8-4270

Mead Johnson PHARMACEUTICALS
A Bristol Myers Company
Evansville, Indiana 47721

# right on TARGET

Consider a few features of **The Western Journal of Medicine:**

- **Epitomes of Progress**
  Each month this selection highlights the major advances in a different specialty with 15 or 20 brief epitomes by experts in the field.
- **Clinical Investigation**
  Five major clinical research societies coordinate important new research findings, emphasizing clinical value.
- **Socioeconomics**
  WJM is often the first to predict, examine, and evaluate socioeconomic changes and trends.
- **Yearly Special Issue**
  Each devoted to a topic vital to physicians: cross-cultural medicine (1983), personal health maintenance (1984), high-tech medicine (1985), medical informatics (1986), AIDS—a global perspective (1987), women and medicine (1988).

Enclosed is $_____ to cover _____ subscriptions.

Subscription renewal ☐ Regular subscription ☐
Foreign subscription ☐ Bill me ☐
Student ☐ Resident ☐

TO: _____

Street _____

City/State/Zip _____

Specialty (If applicable) _____

Student/Resident Completion Date (Year) _____

Please mail this coupon with enclosed payment to:

**Circulation Department**
P.O. Box 7602, San Francisco
California 94120-7602

Subscriptions, 12 issues per year
U.S. and Canada: $30 1 year, $50 2 years
All other countries: $50 1 year, $90 2 years
Student/Resident (USA and Canada): $15 per year

**The Western Journal of Medicine**

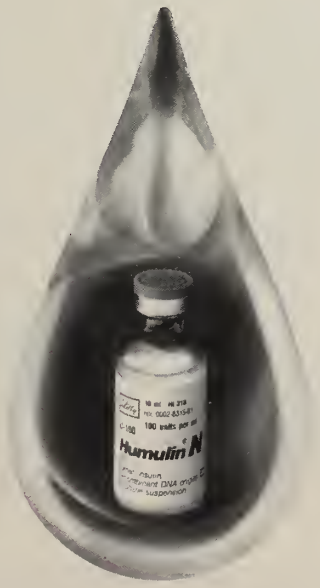
**P.O. Box 7602 • San Francisco, California 94120-7602**
**(415) 882-5179**

For treatment of diabetes:

Introducing
Humulin® 70/30
70% human insulin isophane suspension
30% human insulin injection
(recombinant DNA origin)

# REPLACE
## Human Insulin

## With Human Insulin




Humulin®
human insulin
(recombinant DNA origin)

*Any change of insulin should be made cautiously and only under medical supervision.*

Lilly
Leadership
In Diabetes Care

(Continued from Page 352)

411 **Therapeutic Insemination by Donor**
LEE R. HICKOK, MD

412 **Update on $\alpha$-Fetoprotein Screening in California**
GEORGE CUNNINGHAM, MD

413 **Testing for Chlamydial Infection**
A EUGENE WASHINGTON, MD, MSc

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON, MA
APR 20 1990

## EDITORIALS

414 **Three Possible Futures for Medicine**

414 **Hypertension in the Elderly**
WILLIAM McFATE SMITH, MD
*From the University of California, Berkeley, School of Public Health, and the Department of Epidemiology and International Health, University of California, San Francisco, School of Medicine.*

## CASE REPORTS

417 **Erythrocytosis Caused by an Erythropoietin-Producing Breast Adenocarcinoma**
ROBERT F. BOHNEN, MD; MUSSA BANISADRE, MD; ROLF N. GULBRANDSON, MD; and ESMAIL D. ZANJANI, PhD
*From the Departments of Medicine and Surgery, Roseville Community Hospital, Roseville, California, and the Departments of Medicine and Physiology, Veterans Administration Medical Center, Reno, Nevada.*

418 **Prenatal Diagnosis of Noonan's Syndrome in a Female Infant With Spontaneous Resolution of Cystic Hygroma and Hydrops**
LUIS IZQUIERDO, MD; ORI KUSHNIR, MD; DIANE SANCHEZ, MD; LUIS CURET, MD; PATRICIA OLNEY, MS; GLORIA E. SARTO, MD, PhD; CAROL CLERICUZIO, MD; and RICHARD OLNEY, MD
*From the Departments of Obstetrics and Gynecology and Pediatrics, University of New Mexico Hospital, Albuquerque, and the Department of Pediatrics, Gallup Indian Medical Center, Gallup, New Mexico.*

421 **Chylothorax and Respiratory Failure in Kaposi's Sarcoma**
DANIEL W. PENNINGTON, MD; MARTHA L. WARNOCK, MD; and MICHAEL S. STULBARG, MD
*From the Departments of Medicine and Pathology, Cardiovascular Research Institute, University of California, San Francisco, School of Medicine.*

423 **Fatal Pulmonary Infection With *Mycobacterium fortuitum***
JOSEPH M. NUSSBAUM, MD, and P. N. R. HESELTINE, MD
*From the Department of Internal Medicine, Section of Infectious Disease, Los Angeles County-University of Southern California Medical Center, Los Angeles.*

## CORRESPONDENCE

426 **Asthma Deaths**
JOHN T. CHIU, MD

426 **Thymic Carcinoid and Multiple Endocrine Neoplasia**
DOUGLAS W. BLAYNEY, MD

426 **Iatrogenic Illness**
TERENCE M. DAVIDSON, MD

427 **The War on Drugs**
R. LAWRENCE GIBSON, MD

427 **The Eye of the Beholder**
GERARD N. BURROW, MD

427 **Tryptophan Use and Fasciitis**
BRUCE T. ADORNATO, MD; YUAN CHANG, MD; DIKRAN HOROUPIAN, MD; MAIE HERRICK, MD; ELAINE LAMBERT, MD; GEORGE V. LAWRY, MD; and MARTIN STEIN, MD

428 **Integration of Prevention Efforts**
KENNETH W. KIZER, MD, MPH; JAMES A. FELTEN, MPA; VAUGHN A. JODAR; HIROSHI E. YAMAMOTO; and JEAN M. MONTES

429 **Life-Style and Illness**
IRA E. BAILIE, MD

(Continued on Page 359)

ONCE-A-DAY

# Calan® SR

(verapamil HCl)

180mg

240mg

SUSTAINED-RELEASE **CAPLETS**

## BEYOND YOUR EXPECTATIONS:

## SINGLE-AGENT SUCCESS!*[1-6]

**New recommended starting dose**
for newly diagnosed hypertensives†...
**NEW 180-mg CAPLET once daily**

**SEARLE**

*In mild to moderate hypertension.

†Lower initial doses of 120 mg a day may be warranted in patients who may have an increased response to verapamil (eg. the elderly or small people). Please see next page of this advertisement for references and a brief summary of prescribing information.

© 1990, G.D. Searle & Co. A90-W142T

# 80% SINGLE-AGENT SUCCESS

## ☐ SIX CLINICAL TRIALS ☐ MORE THAN 4,000 PATIENTS ☐ REGARDLESS OF AGE* OR RACE

| Success Rate | Author | Patient Population | Age Range | Goal DBP | Duration of Therapy |
|---|---|---|---|---|---|
| 82% | Reinfrank et al[1] | 97 patients; mild, moderate, severe, and isolated systolic HT | 18-70 | <95 mm Hg | 12 weeks |
| 83% | Saunders et al[2] | 54 black patients; mild to maderate HT | 18-70 | <90 mm Hg or ≥10 mm Hg reduction | 8 weeks |
| 84% | Speders et al[3] | 3,741 patients; mild, moderate, and severe HT | 30-70 | ≤90 mm Hg | 6 weeks |
| 84% | Henry et al[4] | 51 patients; mild to moderate HT | 21-75 | ≤90 mm Hg ar ≥15 mm Hg reduction | 4 months |
| 86% | Midtbo et al[5] | 22 patients; mild to moderate HT | 33-64 | <90 mm Hg | 4 weeks |
| 88% | Bachsler et al[6] | 43 patients; mild to moderate HT | 21-70 | ≤90 mm Hg ar ≥15 mm Hg reductian | 4 months |

HT = hypertension
*For odult hypertensives only.

Constipation, which can be easily managed in most patients, is the most frequently reported side effect of Calan SR.

ONCE-A-DAY **Calan® SR** (verapamil HCl) 180mg 240mg
SUSTAINED-RELEASE CAPLETS

## THE 80% SOLUTION

**BRIEF SUMMARY**

**Contraindications:** Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

**Warnings:** Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

**Precautions:** Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

**Adverse Reactions:** Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence.

12/21/89 • P90-W198V


**References:**
**1.** Reinfrank J, Eckardt A, Schneider G, et al: Long-term efficacy and safety of verapamil SR 240 mg in hypertension. *Acta Therapeutica* 1989;15:221-235. **2.** Saunders E, Weir MR, Kang BW, et al: A comparison of the efficacy and safety of a beta blocker, calcium channel blocker, and converting enzyme inhibitor in hypertensive blacks. *Arch Intern Med* (accepted for publication). **3.** Speders S, Sosna J, Schumacher A, et al: Efficacy and safety of verapamil SR 240 mg in essential hypertension: Results of a multicentric phase IV study. *J Cardiovasc Pharmacol* 1989;13 (suppl 4):S47-S49. **4.** Henry JA, Chester PC, Lathom AN: Sustained-release verapamil or atenolol in essential hypertension. *J Drug Dev* 1988;1:69-75. **5.** Midtbo KA, Hals O, Lauve O: A new sustained-release formulation of verapamil in the treatment of hypertension. *J Clin Hypertens* 1986;3:125S-132S. **6.** Bachsler JA, Simmons RL, Ward PJ, et al: Verapamil SR and propranolol LA: A comparison of efficacy and side effects in the treatment of mild to moderate hypertension. *J Hum Hypertens* 1988;1:305-310.


A90-W142T

SEARLE

G D Searle & Co
Box 5110, Chicago, IL 60680

*Address medical inquiries to:*
*G D. Searle & Co.*
*Medical & Scientific Information Department*
*4901 Searle Parkway*
*Skokie, IL 60077*

(Continued from Page 356)

## TOPICS IN PRIMARY CARE MEDICINE

430 **Dupuytren's Disease**
STEVEN M. GONZALEZ, MD, and RICHARD I. GONZALEZ, MD
*From the Department of Surgery, Stanford University School of Medicine, Stanford, California.*

## HEALTH CARE DELIVERY

434 **Health Care Needs and Services for Technology-Dependent Children in Developmental Centers**
LUCY S. CRAIN, MD, MPH; DONALD N. MANGRAVITE, MD, MPH; ROBERT ALLPORT, MD; MARIANNE SCHOUR, MD, MPH; and KRIST BIAKANJA, MD
*From the Department of Pediatrics, University of California, San Francisco, School of Medicine, and the Committee on Children With Disabilities, Chapter 1, District IX, American Academy of Pediatrics.*

## RADIOLOGIC CASE

439 **A 36-Year-Old Woman With a Pulsatile Mass of the Left Tympanic Membrane**
JODY REISER; KELVIN S. DANIELSON, MD; JONATHAN M. LEVY, MD; RICHARD D. ZONIS, MD; and FRED K. CHRISTENSEN, MD
*Ms Reiser is a fourth-year medical student at the University of Arizona Health Sciences Center, Tucson. From the Departments of Diagnostic Radiology, Otolaryngology, and Neurosurgery, Scottsdale Memorial Hospital, Scottsdale, Arizona.*

## IN THE FOREFRONT

441 **Developing Principles for Prudent Health Care Allocation—The Continuing Oregon Experiment**
RALPH CRAWSHAW, MD; MICHAEL GARLAND, DScRel; BRIAN HINES, MSW; and BARRY ANDERSON, PhD
*From the Departments of Psychiatry and Public Health and Preventive Medicine, Oregon Health Sciences University School of Medicine, and the Department of Psychology, Portland State University, Portland. Mr Hines is a health policy consultant in Salem, Oregon.*

## MEDICAL ETHICS

447 **A Policy Concerning the Therapeutic Use of Human Fetal Tissue in Transplantation**
ROBERT M. NELSON, MD
*From the Division of Pediatric Critical Care, Department of Pediatrics, and the Program in Medical Ethics, University of California, San Francisco, School of Medicine.*

## LESSONS FROM THE PRACTICE

449 **The Trivia Champ and Honorary Faculty Member**
WILLIAM B. SHORE, MD
*From the Department of Family and Community Medicine, Family Practice Residency Program, University of California, San Francisco, School of Medicine, and San Francisco General Hospital.*

## OTHER FEATURES

354 **Subscription Information**
362 **Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming**
450 **Book Reviews**
451 **Information for Authors**
453 **Classified Advertising**
464 **Western State Medical Associations' Meetings**

★ **Official Journal of the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.**

★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

## Moratorium on the Medical Practice Opinion Program

In April of 1989, the California Medical Association's Council imposed a moratorium on the CMA's medical practice opinion program in order to assess the costs of the program against its benefits. Subsequently, the Council voted to create a task force to address the various options for the structure and goals of that program. That task force is now in the process of forming its recommendations. Accordingly, the future of this program is uncertain.

Because, due to the moratorium, the opinions could not be updated, all medical practice opinions rendered by the program have been withdrawn and are no longer in effect. Organizations that currently have programs addressing medical practice questions include:

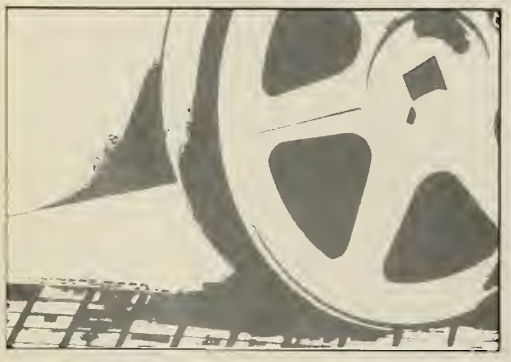
American Medical Association
Diagnostic and Therapeutic Technology Assessment Program
(312) 645-4530
and
American College of Physicians
Clinical Efficacy Assessment Project
(215) 351-2400

Additionally, the Council of Health Care Technology has published a directory entitled the *Medical Technology Assessment Directory* that contains a broad selection of healthcare assessment programs. The Council can be reached at:

Council on Health Care Technology
Institute of Medicine
2101 Constitution Avenue
NW Washington, CA 20418

THE CALIFORNIA MEDICAL ASSOCIATION


**This Publication is available in Microform.**



**University Microfilms International**

Please send additional information
for _____ (name of publication)
Name _____
Institution _____
Street _____
City _____
State _____ Zip _____
300 North Zeeb Road, Dept P.R., Ann Arbor, Mi. 48106

**Just a fraction of what we spend dining out could help pick up the tab for a good cause.**

It's so easy to help your community, when you think about it.

Millions of people have helped make five percent of their incomes and five hours of volunteer time per week the standard of giving in America.

Get involved with the causes you care about and give five.

**Give Five.** *What you get back is immeasurable.*

# PRO TECTION

## MALPRACTICE COVERAGE AT ITS BEST

- Effective and experienced management.
- An improved cash flow position immediately.
- $1 million per occurrence/$3 million aggregate per year.
- Affordable retroactive coverage.
- Remedial medical services designed to alleviate adverse medical/surgical results.

## COMPARE AND SAVE

For further information, please call or write:

PHYSICIANS
INTERINDEMNITY

310 E. Colorado Street, Suite 308, Glendale, California 91205-1633
(818) 241-5119

# Continuing Medical Education

**ARIZONA • CALIFORNIA, HAWAII, NEVADA • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING**

## ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

March 27-30—**15th Annual Primary Care Update.** Arizona Health Sciences Center, Tucson. Tues-Fri. Contact: Lynne Mascarella, (602) 626-7832.

March 29-30—**Clinical Reviews.** Mayo Clinic-Scottsdale at The Registry Resort, Scottsdale. Thurs-Fri. Contact: Mayo Clinic-Scottsdale.

March 31—**Nutrition Update for Primary Care Providers.** Arizona Health Sciences Center, Tucson. Sat. Contact: Lynne Mascarella, (602) 626-7832.

March 31—**Primary Management of Common Cardiovascular Conditions.** Mayo Clinic-Scottsdale at The Registry Resort, Scottsdale. Sat. Contact: Mayo Clinic-Scottsdale.

April 9-14—**Primary Care Update.** Tucson. Mon-Sat. Contact: Cristy Snow, (602) 626-7946.

April 20-21—**Series I—Coronary Heart Disease Update.** Medical Education Resources at La Posada Resort, Scottsdale. Fri-Sat. Contact: Deborah Helton, 1 (800) 421-3756.

April 21—**26th Annual Arizona Chest Symposium.** Tucson Medical Center, Tucson. Sat. Contact: Susan Thornton, (602) 324-1879.

May 4—**Infectious Diseases Update: 1990.** Mayo Clinic-Scottsdale. Fri. Contact: Shelia Collins, (602) 391-8300.

May 11-13—**Allergy and Pregnancy Seminar: 1990.** Greater Phoenix Allergy Society at The Registry Resort, Scottsdale. Fri-Sun. Contact: Merle S. Scherr, MD, (602) 994-9514.

May 14-18—**22nd Annual Southwestern School for Behavioral Health Studies.** University of Arizona, Tucson. Mon-Fri. Contact: Susan Villaescusa, (602) 721-3838.

June 22-24—**Thirteenth Annual Pediatrics in the Red Rocks.** American Academy of Pediatrics—Arizona Chapter at Los Abrigados, Sedona. Fri-Sun. Contact: Melanye Wrighton, (602) 230-1949.

### CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

## CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

### ANESTHESIOLOGY

May 17-20—**California Society of Anesthesiologists 1990 Annual Meeting.** California Society of Anesthesiologists at San Francisco Marriott. Thurs-Sun. 18 hrs. $175. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

May 29-June 3—**UCSD Anesthesiology Review Course.** UCSD at San Diego Princess, San Diego. Tues-Sun. Contact: UCSD.

September 8-9—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Lake Tahoe, California. Sat-Sun. 20 hrs. $175. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

### CARDIOLOGY

April 28—**Current Concepts in Heart Disease.** Grossmont Hospital at Bahia Hotel, San Diego. Sat. 6 hrs. $100. Contact: Continuing Medical Education, Grossmont Hospital, PO Box 158, La Mesa 92044. (619) 589-4153.

May 4-5—**Series II—Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Marriott Hotel, San Diego. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

May 5-6—**The Cardiac Patient: Current Controversies and Clinical Decision Making.** Saddleback Memorial Medical Center's Heart Institute at Four Seasons Hotel, Newport Beach. Sat-Sun. $150. Contact: Saddleback Memorial Education Department, (714) 837-4500, ext 3639.

June 15-16—**Series IV—Cardiac Wellness and Rehabilitation.** Medical Education Resources at Hyatt Union Square, San Francisco. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

June 22-23—**Series I—Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

August 3-4—**Series II—Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Anaheim. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

August 17-18—**Series IV—Cardiac Wellness and Rehabilitation.** Medical Education Resources at Monterey. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

### DERMATOLOGY

June 8-9—**Southwestern Regional Cutaneous Flap Workshop.** UCLA. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

June 8-9—**Advances in Skin Cancer Management: A Multi-Specialty Approach.** UCSF at Portman Hotel, San Francisco. Fri-Sat. 10 hrs. $250. Contact: UCSF.

August 3-4—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

August 16-19—**Advanced Seminars in Dermatology.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sun. Contact: UCSD.

*(Continued on Page 364)*

# Exceptional Ambulatory Care Facilities . . .

**Casa Blanca Clinic, Ltd.**

**Multi-Specialty Group Practice and Ambulatory Surgery Center**

Stan Decker Administrator
James Liguori, M.D. Medical Director

SIMMONDS

## The Specialists In Medical Facility Development.

**Saint Louis, Missouri ▪ Mercer Island, Washington ▪ Newport Beach, California**

**206•236•0800**

CONTINUING MEDICAL EDUCATION

(Continued from Page 362)

## EMERGENCY MEDICINE

April 19-22—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal, Series 3.** Emergency Medical Abstracts at San Francisco. Thurs-Sun. 20 hrs. Contact: Robert Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

May 7-11—**Emergency Medicine Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $450. Contact: UCSD.

May 16-20—**12th Annual: Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

May 27-31—**Annual Scientific Assembly.** California Chapter of the American College of Emergency Physicians at Silverado Country Club, Napa. Sun-Thurs. 18 hrs. CAL/ACEP, (213) 374-4039.

June 25-29—**Emergency Medicine Symposium III: Pediatrics.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $450. Contact: UCSD.

August 1-5—**Wilderness Medicine: '90.** American College of Emergency Physicians at Squaw Valley Lake Tahoe, Nevada. Wed-Sun. 22 hrs. $395. Contact: Eugene Allred, MD, PO Box 321, Yreka 96097 (800) 888-5632.

August 20-24—**Emergency Medicine Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $450. Contact: UCSD.

## FAMILY PRACTICE/PRIMARY CARE

April 18-20—**40th Annual Course for Physicians in Family Practice: Practice in the 1990s.** Wed-Sat. Contact: Mary P. Arnold, Mount Zion Hospital and Medical Center, PO Box 7921, San Francisco 94120. (415) 885-7270.

June 3-8—**14th Annual Fingers to the Toes: Primary Care Orthopaedics.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. Contact: UCD.

June 11-15—**UCI Family Practice Refresher Course.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. Mon-Fri. 29 hrs. Contact: UCI.

July 9-12—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Thurs. 25 hrs. Contact: UCSF.

## INTERNAL MEDICINE

April 18-20—**Advances in Infectious Diseases.** UCSD at Fairmont Hotel, San Francisco. Wed-Fri. 18 hrs. $380. Contact: UCSF.

April 21—**5th Annual Conference: New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at Amphitheater of the Green Hospital, Scripps Clinic, La Jolla. Sat. $125. Contact: Bonny Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 14-18—**Hyperbaric Medicine.** UCI/Memorial Medical Center. 36 hrs. $650. Contact: Celia Loney, (213) 595-3613.

May 18-20—**8th Symposium on Frontiers of Rheumatology.** Annenberg Center for Health Sciences. Fri-Sun. Contact: ACHS, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 321-3690.

June 11-15—**Advances in Internal Medicine.** UCSF at San Francisco Marriott Hotel. Mon-Fri. 33 hrs. $535. Contact: UCSF.

June 25-30—**Advances in Internal Medicine.** UCSF at Cole Hall, San Francisco. Tues-Sat. 32 hrs. $535. Contact: UCSF.

September 14-16—**Gastroenterology.** UCSF at Portman Hotel, San Francisco. Fri-Sun. 17 hrs. $415. Contact: UCSF.

(Continued on Page 366)

# Applications Invited for Board Certification

A time limited **grandfathering** is presently in effect until December 1991. Three levels of certification are available: "Diplomate," "Fellow," and "Clinical Associate," depending upon amount and type of education and work experience in fields related to pain management.

Physicians, dentists, psychologists, and other health care providers who have been granted a doctorate from an accredited university and who have two years of approved clinical experience may apply for the **Diplomate Credential.**

Individuals trained at the Masters level in related health care disciplines with two years of approved experience may apply for the **Fellow Credential.**

Individuals with a Baccalaureate Degree or its equivalent and five years of experience may apply for the **Clinical Associate Credential.** All applicants must have significant work experience in pain management.

During the grandfathering period, educational degrees earned from accredited training programs and relevant professional work experience will be considered. The Board will review applications on an individual case basis for appropriateness. Certification is dependent upon adherence to the ethical standards of the Academy. Certified providers must demonstrate ongoing professional development.

Please send me an application form and information packet.

Name _____

Address _____

Phone (_____) _____

AMERICAN ACADEMY
OF PAIN MANAGEMENT
3600 Sisk Road
Suite 2-D
Modesto, CA 95356

"I toss dozens of journals. Senior Patient is one I keep."

Senior Patient is the readable journal that helps me with the frustrating problems of older patients.

Be sure to read every issue from cover to cover.

4530 W. 77th Street • Minneapolis, MN 55435 • (612) 835-3222 McGraw Hill

CONTINUING MEDICAL EDUCATION

(Continued from Page 364)

## OB/GYN

April 19-20—**Prenatal Genetics Diagnosis and Fetal Therapy.** UCI at Red Lion Hotel, Costa Mesa. Thurs-Fri. Contact: UCI.

April 28—**Symposium on Gynecologic Oncology.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Bonny Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

June 1-3—**Advanced Fetal Heart Rate Monitoring.** UCI at Monterey Plaza Hotel. Fri-Sun. Contact: UCI.

June 8-10—**Perinatal High Tech: A Brave New World.** Perinatal Advisory Council of Los Angeles at Fess Parker's Red Lion Resort, Santa Barbara. Fri-Sun. 16 hrs. $150. Marianne Gray, 3600 Wilshire Blvd, Ste 600, Los Angeles 90010. (213) 380-1790.

August 17-19—**3rd Annual Perinatal Review.** Memorial/UCI Center for Health Education at Four Seasons Hotel, Newport Beach. Fri-Sun. Contact: UCI.

August 21-25—**8th Annual Controversies in OB/GYN.** Memorial/UCI Center for Health Education at Mauna Kea, Hawaii. Tues-Sat. Contact: UCI.

## OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

May 31-June 1—**Occupational and Environmental Medicine.** UCD at Capitol Plaza Holiday Inn, Sacramento. Fri-Sat. Contact: UCD.

## OPHTHALMOLOGY

May 25-28—**California Association of Ophthalmology: 9th Annual Educational Conference.** California Association of Ophthalmology at Doubletree Hotel Fisherman's Wharf, Monterey Conference Center. Fri-Mon. 6 hrs. $275. Contact: CAO, 605 Market St, Ste 1109, San Francisco 94105. (415) 777-3937.

## PATHOLOGY

May 24-25—**Current Issues in Anatomic Pathology: 1990.** UCSF at Union Square Holiday Inn, San Francisco. Thurs-Fri. 12 hrs. $300. Contact: UCSF.

May 26—**Fine Needle Aspiration Tutorials.** UCSF. Sat. 7 hrs. $550. Contact: UCSF.

## PEDIATRICS

April 19-20—**9th Annual Child Abuse.** UCD at Radisson Hotel, Sacramento. Thurs-Fri. 12 hrs. $135. Contact: UCD.

May 17-19—**23rd Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 16 hrs. $300. Contact: UCSF.

June 29-30—**Current Concepts in Pediatric Allergy and Otolaryngology.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sat. Contact: Continuing Medical Education Office, Children's Hospital, (619) 576-4072.

September 7-8—**Pediatrics and Environmental Health: The Pediatrician as Investigator, Educator, and Advocate.** Children's Hospital Oakland at Berkeley Conference Center. Fri-Sat. 12 hrs. $85. Contact: Joy Carlson, EPI Training Project, 5900 Hollis St, No E, Emeryville 94608. (415) 540-3657.

## PREVENTIVE MEDICINE

June 3—**Therapeutic Frontiers.** UCLA at Miramar Sheraton Hotel, Santa Monica. Sun. 6 hrs. $50. Contact: UCLA.

## PSYCHIATRY

April 23-27—**Introduction to Medical Hypnosis.** UCSD at The Inn at Del Mar. Mon-Fri. Contact: UCSD.

April 28-29—**The Cutting Edge 1990—The Heart of the Matter: Helping Improve Relationships.** UCSD at La Jolla Marriott Hotel. Fri-Sat. 13 hrs. $300. Contact: Cass Jones, 7916 Convoy Court, San Diego 92111. (619) 565-9921.

May 19—**Ideomotor Techniques in Hypnotherapy.** Southern California Society of Clinical Hypnosis at UCLA Neuropsychiatric Institute, Los Angeles. Sat. 5 hrs. Contact: Karnie Starrett, 10840 Queensland St, Los Angeles 90034. (213) 475-1260.

June 8-9—**The Threat to the Cosmic Order: Psychological, Social, and Health Implications of Richard Wagner's Ring of the Nibelung.** UCSF at Laurel Heights Campus, San Francisco. Fri-Sat. Contact: UCSF.

## RADIOLOGY

April 15-20—**10th Annual San Diego Residents Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 39 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 21—**Introduction to Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8 hrs. $100. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

May 22-25—**CT and MRI in Body Imaging: A Comprehensive Course.** Tues-Fri. 15 hrs. $515. Contact: UCSF.

June 12-16—**Computer Assisted Radiology.** UCI at Anaheim Hilton Hotel. Tues-Sat. Contact: UCI.

July 22-26—**Napa Valley Imaging Update: MRI 1990.** UCD at Silverado Country Club, Napa. Sun-Thurs. 17 hrs. $445. Contact: UCD.

July 23-25—**Musculoskeletal Imaging.** Hoag Memorial Hospital, Department of Radiology at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Wed. 15 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 26-29—**4th Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital, Department of Radiology at Ritz-Carlton Resort Hotel, Laguna Niguel. Thurs-Sun. 22 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 23-28—**6th Annual Physics and Biology of Radiology.** UCSD at Hanalei Hotel, San Diego. Thurs-Tues. 25 hrs. $395. Contact: UCSD.

September 7-10—**6th Annual Sonography Update for Physicians and Sonographers.** UCSD at Hotel del Coronado, San Diego. Fri-Mon. 18 hrs. $375. Contact: UCSD.

## SURGERY

April 1990-December 1990—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

April 1990-June 1990—**Microsurgery Training Courses.** UCSD at Grossmont Hospital, La Mesa. 40 hrs. $1125. Contact: UCSD.

April 19-20—**General Thoracic Surgery.** American College of Chest Physicians at Tropicana Hotel, Las Vegas. Thurs-Fri. 13 hrs. $275. Contact: ACCP, 911 Busse Hwy, Park Ridge, IL 60068. (708) 698-2200.

April 26-28—**Postgraduate Course in General Surgery.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 15 hrs. $300. Contact: UCSF.

May 19—**Prosthetics-Orthotics Course.** UCD at UCD Medical Center, Sacramento. Sat. Contact: UCD.

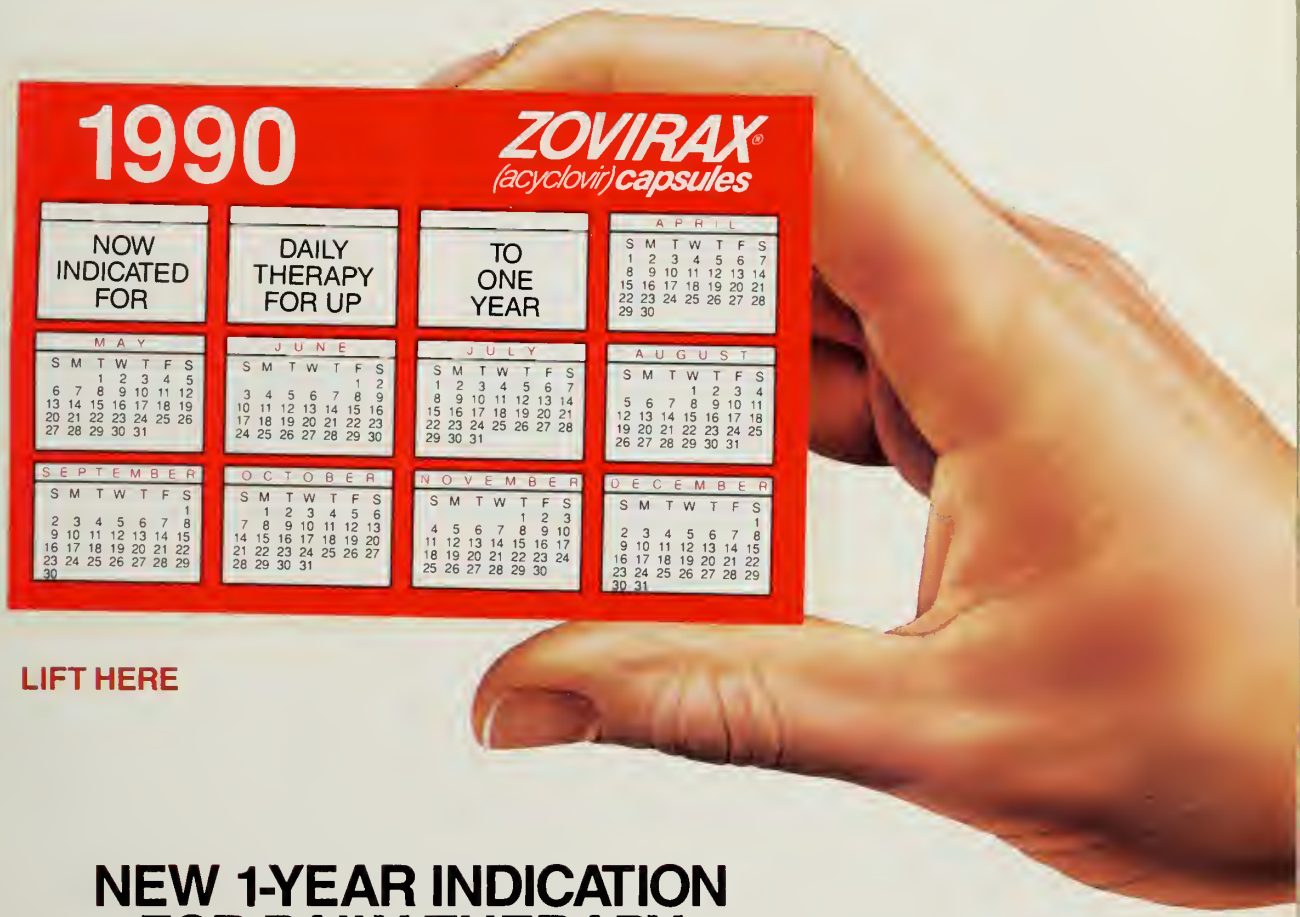
June 17-22—**Anatomic Basis for Aesthetic Surgery: Hands-On Laboratory Course.** UCD at Hyatt Regency, Sacramento. Sun-Fri. Contact: UCD.

June 21-23—**7th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Medical Center at La Jolla Marriott Hotel. Thurs-Sat. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 598-0080.

July 17-21—**6th Annual Superficial Anatomy and Cutaneous Surgery.** UCSD at La Jolla Marriott. Tues-Sat. Contact: UCSD.

(Continued on Page 371)

# ANNOUNCING A GREAT YEAR AHEAD FOR HERPES PATIENTS




## NEW 1-YEAR INDICATION FOR DAILY THERAPY

Herpes patients can look forward to a great year ahead. Results of a recent clinical study show a lesion-free year for nearly half the patients treated with ZOVIRAX Capsules 400 mg b.i.d.[†][1] For all ZOVIRAX Capsule recipients, recurrences during the study year were limited to a mean of 1.8, compared with a mean of 11.4 for placebo recipients.[1]

Daily use was also shown to be well tolerated. And this extended clinical study demonstrated no evidence of cumulative toxicity and no change in acyclovir sensitivity.[1,2]

Prescribe daily ZOVIRAX Capsule therapy...and help keep your patients lesion-free longer.*

**References: 1.** Mertz GJ, Jones CC, Mills J, et al Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection a multicenter double-blind trial *JAMA* 1988,260 201-206 **2.** Mertz GJ, Eron L, Kaufman R, et al Prolonged continuous versus intermittent oral acyclovir treatment in normal adults with frequently recurring genital herpes simplex virus infection *Am J Med* 1988,85(suppl 2A) 14-19 **3.** Data on file, Burroughs Wellcome Co , 1990

*In a controlled study of 3 years' duration, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively[3]

[†]Alternate maintenance regimens range from 200 mg t i d to 200 mg five times daily

**ZOVIRAX®**
*(acyclovir)* **capsules**

Please see brief summary of prescribing information on next page

# ZOVIRAX®
## (acyclovir) capsules

## Daily therapy keeps herpes patients lesion-free longer*

Brief Summary

**INDICATIONS AND USAGE:** Zovirax Capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional and psychosocial difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus Zovirax Capsules are not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories:

**First Episodes** (primary and nonprimary infections—commonly known as initial genital herpes):

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax.

**Recurrent Episodes:**

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that Zovirax Capsules given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients.

In a study of 283 patients who received 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52% and 63% of patients remained free of recurrences in the first, second and third years, respectively. Serial analyses of the 3 month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time.

The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of acyclovir therapy. Re-evaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy. Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year.

Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, Zovirax Capsules should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients with annual re-evaluation.

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

**CONTRAINDICATIONS:** Zovirax Capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

**WARNINGS:** Zovirax Capsules are intended for oral ingestion only.

**PRECAUTIONS: General:** Zovirax has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS — Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of Herpes simplex isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of Herpes simplex virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY-Microbiology).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

**Drug Interactions:** Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced. The clinical effects of this combination have not been studied.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg given by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. In 2 *in vitro* cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive life-time bioassays in rodents, conflicting results were obtained. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative in another transformation system considered less sensitive.

In acute studies, there was an increase, not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats but not Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found after 5 days dosing in a dominant lethal study in mice. In 6 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed. At 3 loci in a Chinese hamster ovary cell line, the results were inconclusive. In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells *in vitro*), positive responses for mutagenicity and chromosomal damage occurred, but only at concentrations at least 400 times the acyclovir plasma levels achieved in man.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). At 50 mg/kg/day s.c. in the rat, there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day. No effect upon implantation efficiency was observed when the same dose was administered intravenously. In a rat peri- and postnatal study at 50 mg/kg/day s.c., there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the $F_1$ generation. Although not statistically significant, there was also a dose related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size. However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits, there were no drug-related reproductive effects.

Intraperitoneal doses of 320 or 80 mg/kg/day acyclovir given to rats for 1 and 6 months, respectively, caused testicular atrophy. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. Testicles were normal in dogs given 50 mg/kg/day i.v. for one month.

**Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.) or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures provided plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity. In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation day 10, providing plasma levels 63 and 125 times human levels. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

**Nursing Mothers:** Acyclovir concentrations have been documented in breast milk in two women following oral administration of Zovirax and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when Zovirax is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS—Short-Term Administration:** The most frequent adverse reactions reported during clinical trials of treatment with Zovirax Capsules were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with Zovirax Capsules (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

**Long-Term Administration:** The most frequent adverse reactions reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 Zovirax – treated patients were: nausea (4.8%), diarrhea (2.4%), headache (1.9%) and rash (1.7%). The 589 control patients receiving intermittent treatment of recurrences with Zovirax for 1 year reported diarrhea (2.7%), nausea (2.4%), headache (2.2%) and rash (1.5%).

The most frequent adverse reactions reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%) and paresthesia (0.8%). Reactions reported by 329 patients during the third year include asthenia (1.2%), paresthesia (1.2%) and headache (0.9%).

**DOSAGE AND ADMINISTRATION: Treatment of initial genital herpes:** 200 mg every 4 hours, 5 times daily for 10 days.

**Chronic suppressive therapy for recurrent disease:** 400 mg 2 times daily for up to 12 months, followed by re-evaluation. See INDICATIONS AND USAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

**Intermittent Therapy:** 200 mg every 4 hours, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

**Patients With Acute or Chronic Renal Impairment:** Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment. Based on these studies, a dosage adjustment is recommended for patients with creatinine clearance $\leq 10$ ml/min/1.73 m². For these patients, a 200 mg dose every 12 hours is recommended.

U.S. Patent No. 4199574

* In a controlled study of 3 years' duration, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively.[3]

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

**Burroughs Wellcome Co.,**
Research Triangle Park,
North Carolina 27709

Copr © 1990 Burroughs Wellcome Co.
All rights reserved ZOC-103 January 1990

# COMMITTED TO EXCELLENCE

ROCHE

PRESIDENT'S ACHIEVEMENT AWARD

## Presenting the winners of the 1989 Roche President's Achievement Awards

Roche Laboratories is proud to honor these outstanding sales representatives, chosen for their unparalleled dedication to the healthcare field, professionalism and consistent high level of performance. Please join us in congratulating these exceptional individuals.

Dudley A. Desler

Douglas R. Dewar

Gary P. Ferreria

Eileen S. Gallagher

Jay Tal Gardenhire

Tamara L. Hagen

Susan K. Hemann

M. Jane Higgins

John L. Irving

Sandy L. Josephs

Johnel A. Maryland

Kaye H. Moore

Ryan B. Packard

John R. Pajerski

Jerald S. Parkinson

James E. Peabody

Raymond K. Reutlinger

Russel J. Roe

Donald G. Tatum

Robert F. Thomas

Arnold M. Yee

James E. Zornes, Jr.

Turn to the following page and find out how your award-winning Roche representative can help both you *and* your patients.

# Your Roche Representative Would Like You To Have Something That Will...

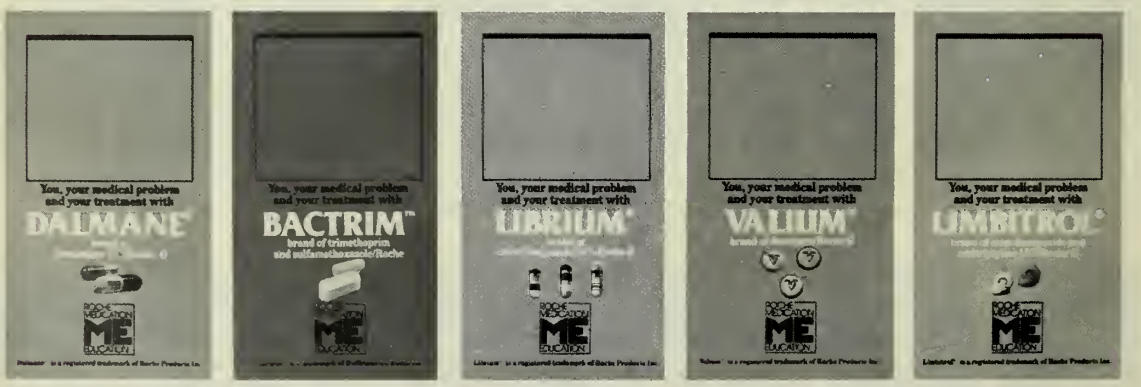
ROCHE®

... improve patient satisfaction with office visits.
... improve patient compliance with your instructions.
... reduce follow-up calls to clarify instructions.

## Roche product booklets ...

- offer a supplement to, not a substitute for, patient contact.
- support your specific instructions to the patient.
- provide a long-term reinforcement of your oral counseling.
- are available in *Spanish*.

Because you are the primary source of medical information for your patients, we invite you to look over the Roche product booklets shown below. Ask your Roche representative for the new catalog brochure of patient education materials and for a complimentary supply of those booklets applicable to your practice, including the WHAT IF Book in large type.




ROCHE ME MEDICATION EDUCATION

Working today for a healthier tomorrow

CONTINUING MEDICAL EDUCATION

(Continued from Page 366)

## OF INTEREST TO ALL PHYSICIANS

April 27—**Alzheimer's Update.** UCD at Beverly Garland Hotel, Sacramento. Fri. 7 hrs. $120. Contact: UCD.

June 21-23—**Nevada State Medical Association Annual Meeting.** Nevada State Medical Association at Hyatt Lake Tahoe, Nevada. Thurs-Sat. Contact: Nevada State Medical Association, 3660 Baker Lane, Reno, NV 89509. (702) 825-6788.

July 9-13—**2nd Annual Marine Medicine.** UCSD at San Diego Princess. Mon-Fri. Contact: UCSD.

July 19-22—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 26 hrs. $295. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077. (404) 641-9773.

July 23-27—**4th Annual Sports Medicine.** UCSD at San Diego Princess. Mon-Fri. Contact: UCSD.

### KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Avenue, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

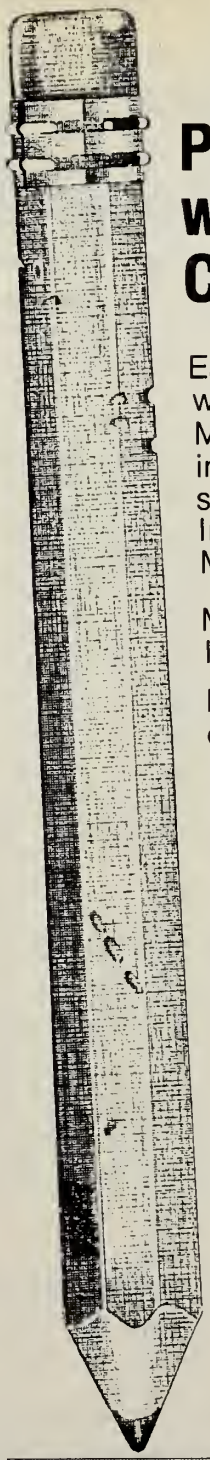
USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

## COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

(Continued on Page 372)

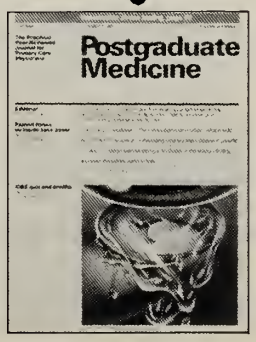
**Pointing the way to more CME credit.**

Earn more CME credit with Postgraduate Medicine's new and improved CME Program sponsored by the Interstate Postgraduate Medical Association.

More CME credits for less money ($10.00).

Practical questions covering the most important points from each article—not just one symposium article.

Now, more than ever, you'll want to read every issue of Postgraduate Medicine from cover to cover!




4530 W. 77th Street
Minneapolis, MN 55435
(612) 835-3222

CONTINUING MEDICAL EDUCATION

(Continued from Page 371)

June 10-16—**35th Annual Family Practice Review.** U of Colo at YMCA of the Rockies, Estes Park. One week. Contact: U of Colo.

June 30-July 3—**Renal Disease for the Internist and Nephrologist.** U of Colo at the Given Institute, Aspen. Sat-Tues. Contact: U of Colo.

July 8-13—**25th Annual Internal Medicine Program.** U of Colo at YMCA of the Rockies, Estes Park. Mon-Fri. Contact: U of Colo.

July 18-21—**Insulin Dependent Diabetes.** Barbara Davis Center for Childhood Diabetes, the Children's Diabetes Foundation, and CU School of Medicine at Keystone Inn, Keystone. Wed-Sat. Contact: U of Colo.

July 23-27—**3rd Annual Colorado Geriatric Symposium.** U of Colo at the Given Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 30-August 3—**Dynamic Psychotherapy.** U of Colo at the Given Institute, Aspen. Mon-Fri. Contact: U of Colo.

August 5-9—**Annual Pediatric Program.** U of Colo at the Given Institute, Aspen. Sun-Thurs. Contact: U of Colo.

August 12-18—**Annual Primary Care Orthopedics.** U of Colo at the Given Institute, Aspen. One week. Contact: U of Colo.

August 14-18—**Aspen Basic/Clinical Science: Neuroscience.** U of Colo at the Given Institute, Aspen. Tues-Sat. Contact: U of Colo.

August 20-24—**Annual Internal Medicine Board Review.** U of Colo, Denver. Mon-Fri. Contact: U of Colo.

September 10-14—**Family Practice Review.** U of Colo, Denver. Mon-Fri. Contact: U of Colo.

### CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

## IDAHO

May 9-12—**Snake River Medical Forum.** Lewiston. Wed-Sat. Contact: Nita Shoemaker, Program Coordinator, St Joseph Regional Medical Center, PO Box 816, Lewiston 83501. (208) 799-5416.

May 17-19—**Idaho Academy of Family Physicians—Annual Meeting.** Red Lion Riverside, Boise. Thurs-Sat. Contact: Mrs Irma Sparks, Exec Dir, Idaho Academy of Family Physicians, PO Box 175, Boise 83701. (208) 362-4808.

July 26-28—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sun. Contact: Idaho Medical Association, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

## NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

May 4-5—**103rd Annual Meeting of the New Mexico Medical Society.** Albuquerque. Fri-Sat. Contact: Glenn Taylor, New Mexico Medical Society, 7770 Jefferson, NE, Albuquerque 87109. (505) 828-0237.

## UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

### MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

April 27-28—**Update in Disorders of the Esophagus** (Sponsor: UUMC). Fri-Sat. Marriott Hotel, Salt Lake City. Contact: (801) 581-8664.

May 3-4—**Ethics and Health** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: (801) 581-8664.

May 11-12—**Update in Hyperlipidemias** (Sponsor: UUMC). Fri-Sat. Holiday Inn, St George. Contact: (801) 581-8664.

June 17-22—**School on Alcoholism and Other Drug Dependencies** (Sponsor: UUMC). Sun-Fri. University of Utah, Salt Lake City. Contact: (801) 538-3956.

July 8-14—**Update in Internal Medicine: Board Review Course** (Sponsor: UUMC). Sun-Sat. Cliff Lodge, Snowbird. Contact: (801) 581-8664.

October 4-5—**Ethics and Health** (Sponsor: UUMC). Thurs-Sat. University of Utah Alumni House, Salt Lake City. Contact: (801) 581-8664.

### SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

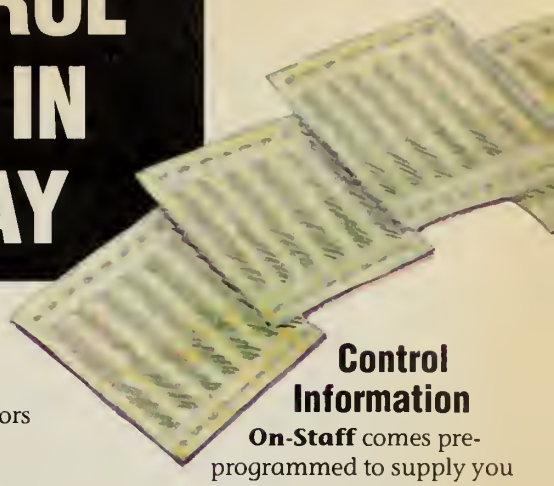
LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

(Continued on Page 374)

# TAKE CONTROL EVERY DAY IN EVERY WAY

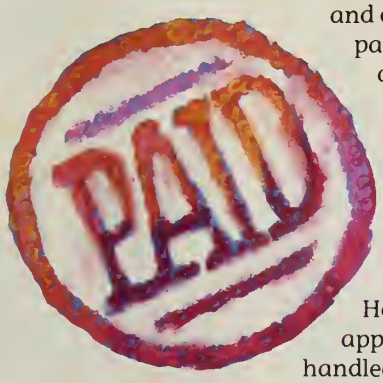


## On-Staff™... for Powerful, Sensible Practice Management

Examine **On-Staff**, the industry's most powerful and easy to use medical practice management system. Whether you're a solo practitioner or manage multi-specialty clinics, **On-Staff** software gives you more ways to control every aspect of your medical practice from patient scheduling to the final payment posting.

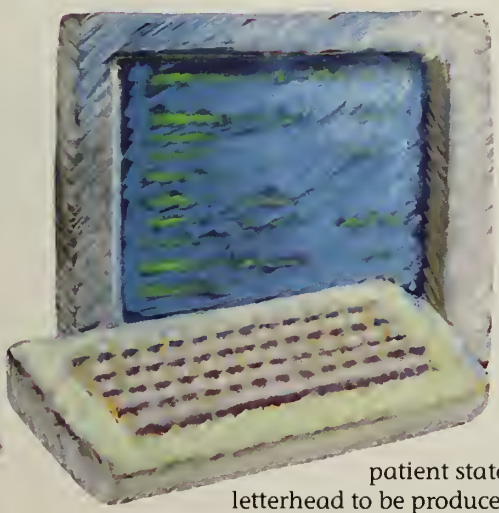
## Control Receivables

**On-Staff** computes the financial responsibilities of insurance carriers versus patients, and effectively monitors payments and adjustments. The system is specifically designed to speed the collection process. **On-Staff** automates not just billing, but also the whole range of follow-up routines. Hence, insurance tracers, appeal letters, etc. are all handled automatically.




## Control Information

**On-Staff** comes preprogrammed to supply you with all the standard reports, but it can also provide you with virtually any other kind of information on demand: you may want a list of patients with a particular ailment within specific zip codes, or wish to identify insurance companies with a bad record of payments. Just define your criteria in plain English, and watch **On-Staff** deliver, instantaneously.



## Control Your Office

**On-Staff** interacts with a variety of wordprocessing and spreadsheet programs to simplify your office work and help you get the most out of your computing investment. **On-Staff's** "forms generator" allows insurance claim forms, patient statements, and even your letterhead to be produced from plain paper.

## Control Communications

**On-Staff** offers a sensitive system for business communication. So, whether it is requesting a patient to meet his deductible, or responding to a denial by an insurance carrier, **On-Staff** generates a precise and personal letter for the right party automatically.

☐ Yes, I would like to take control of my daily administration with a **FREE** demonstration.

☐ Yes, I would like a copy of your **FREE On-Staff** brochure.

☐ No, I would not like to take control. My office is running at peak efficiency.

Best time to call _____ AM/PM

Phone ( ) _____

Name _____

Title _____

Address _____

City _____ State _____ Zip _____

☐ I currently have a computer system in place.

☐ I do not have a computer system in place.

PRIME CLINICAL SYSTEMS, INC.

Prime Clinical
80 South Lake Avenue
Pasadena, CA 91101
**1-800-523-5977**

## Control Your Future

Send in the information card or call toll free 1-800-523-5977 today for a free brochure or an **On-Staff** demonstration to address your specific needs.

IBM Business Partner

On-Staff is a trademark of Prime Clinical Systems.
IBM is a registered trademark of International Business Machines

(Continued from Page 372)

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

## WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

April 27—**Dermatology.** Tacoma. Fri. Contact: (206) 627-7137.

May 4-5—**Orthopedic Review.** Seattle. Fri-Sat. Contact: VMMC.

May 10—**Nutrition.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

May 10-11—**Aggressive Musculoskeletal and Spinal Evaluation, Treatment, and Rehabilitation.** Tacoma. Thurs-Fri. Contact: CME Pierce County.

May 18-19—**Applications of Doppler Ultrasound.** Seattle. Fri-Sat. Contact: VMMC.

June 8-9—**Common Anorectal Disorders: A Medical and Surgical Approach.** Seattle. Fri-Sat. Contact: VMMC.

June 14-15—**Orthopaedics.** Seattle. Thurs-Fri. Contact: Northwest Hospital, (206) 364-0500.

June 16—**AIDS Issues 1990.** Kirkland. Sat. Contact: Evergreen Hospital, (206) 823-7599.

June 25-26—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: CME Pierce County.

September 20—**Orthopedics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

October 11—**Diabetes.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

November 8—**Pediatrics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

### COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

## WYOMING

May 17-19—**Wyoming Academy of Family Physicians—Summer Meeting.** Auditorium, University of Wyoming Family Practice Residency Program, Casper. Thurs-Sat. Contact: Jay Swedberg, MD, 1522 East A St, Casper 82601. (307) 266-3076.

June 14-16—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

August 8-11—**American College of Surgeons, Montana—Wyoming Chapter.** Jackson Hole. Wed-Sat. Contact: Robert C. Ratcliff, MD, 940 E Third St, Casper 82601. (307) 577-4223. ◆


USING IT WON'T KILL YOU. NOT USING IT MIGHT.

Maybe you don't like using condoms. But if you're going to have sex, a latex condom with a spermicide is your best protection against the AIDS virus.

Use them every time, from start to finish, according to the manufacturers' directions. Because no one has ever been cured of AIDS. More than 40,000 Americans have already died from it.

And even if you don't like condoms, using them is definitely better than that.

HELP STOP AIDS. USE A CONDOM.

AMERICAN FOUNDATION FOR AIDS RESEARCH

Ad Council A Public Service of This Publication & The Advertising Council

NATIONAL AIDS NETWORK

Photo: Jerry Friedman ©1988, The Ad Council.

# PUT YOUR MEDICAL CAREER IN FLIGHT.

Discover the thrill of flying, the end of office overhead and the enjoyment of a general practice as an Air Force flight surgeon. Talk to an Air Force medical program manager about the tremendous benefits of being an Air Force medical officer:

- Quality lifestyle, quality practice
- 30 days vacation with pay per year
- Support of skilled professionals
- Non-contributing retirement plan if qualified

Discover how to take flight as an Air Force flight surgeon. Talk to the Air Force medical team today. Call

**USAF**
**HEALTH PROFESSIONS**
**TOLL FREE**
**1-800-423-USAF**

AIR FORCE

# THE FIRST NAME IN QUALITY CARE FOR THE BLACK HYPERTENSIVE

Once-daily 'Dyazide' gives your black patients, as well as your elderly patients, dependable blood pressure control. This plus decades of quality and experience all add up to the first-class care your hypertensive patients deserve.

**DYAZIDE®**
25 mg Hydrochlorothiazide/50 mg Triamterene/SKF

*The Original.*

a product of
**SK&F LAB CO.**
Cidra, P.R. 00639
© SK&F Lab Co., 1989

**DYAZIDE®**
**25 mg Hydrochlorothiazide/50 mg Triamterene/SKF**

***Before prescribing, see complete prescribing information in SK&F LAB CO. literature or PDR. The following is a brief summary.***

***Indications and Usage:*** *Hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone; in patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked.*

*This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.*

*'Dyazide' may be used alone or as an adjunct to other antihypertensive drugs; dosage adjustments may be necessary.*

***Contraindications:*** *Concomitant use with other potassium-sparing agents such as spironolactone or amiloride; potassium supplements (except in presence of severe hypokalemia); anuria, acute and chronic renal insufficiencies or significant renal impairment; hypersensitivity to drug or other sulfonamide-derived drugs; preexisting elevated serum potassium concentration.*

***Warnings:*** *Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium-conserving diuretic combinations, including 'Dyazide'. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving 'Dyazide', when dosages are changed or with any illness that may influence renal function.*

*If hyperkalemia is suspected, obtain an ECG and monitor serum potassium. If hyperkalemia develops, discontinue 'Dyazide' and initiate thiazide therapy if needed. Persistent hyperkalemia may require dialysis. Monitor serum electrolytes frequently in patients with mild renal dysfunction and in diabetic patients. In patients who may develop respiratory or metabolic acidosis, monitor serum electrolytes and acid/base balance frequently.*

***Precautions:*** *The bioavailability of the hydrochlorothiazide and triamterene components of 'Dyazide' is about 50% of the maximum obtainable with oral therapy. Theoretically, a patient transferred from therapy with hydrochlorothiazide with or without triamterene might show an increase in blood pressure, fluid retention, or change in serum potassium. Extensive clinical experience with 'Dyazide', however, suggests that these conditions have not been commonly observed in clinical practice. (See CLINICAL PHARMACOLOGY.) Use thiazides cautiously in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease; potassium depletion induced by the thiazide may be important in this connection; administer 'Dyazide' cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor; if mental confusion increases, discontinue 'Dyazide' for a few days; attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion. If patients develop hypokalemia, which is uncommon with 'Dyazide', increase potassium intake (i.e., with supplements or potassium-rich foods). If repeat determinations show serum potassium concentrations below 3.0 mEq/L, discontinue 'Dyazide' and initiate potassium chloride supplementation. Institute corrective measures cautiously and monitor serum potassium concentrations frequently, especially in patients receiving digitalis or those with a history of cardiac arrhythmias. Diuretics may aggravate existing electrolyte imbalances, especially at high dosages or in patients on salt-restricted diets. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Chloride replacement may be required in the treatment of metabolic acidosis. If dilutional hyponatremia develops, restrict water intake. In actual salt depletion, initiate sodium chloride replacement. Use 'Dyazide' cautiously in patients with a history of renal stone formation.*

*If hyperkalemia develops when treating for hypokalemia, take corrective measures. Also discontinue 'Dyazide' and, if appropriate, substitute a thiazide diuretic until potassium levels return to normal. Do periodic BUN and serum creatinine determinations, especially in the elderly and in patients with suspected or confirmed renal insufficiency. Serum PBI levels may decrease without signs of thyroid disturbance. Discontinue thiazides before conducting parathyroid function tests.*

*Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine; therefore use cautiously in patients undergoing surgery. Monitor electrolytes in patients taking amphotericin B, corticosteroids or corticotropin concomitantly. Thiazides may potentiate the action of other antihypertensive drugs. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be needed. 'Dyazide' may raise the level of blood uric acid; dosage adjustments of antigout medication may be needed to control hyperuricemia and gout. The following agents given with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq of potassium per liter of whole blood when stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium), and salt substitutes (most contain substantial amounts of potassium). Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium concentrations by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake. Chronic or overuse of laxatives may reduce serum potassium concentrations by promoting excessive potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene. The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine. 'Dyazide' will interfere with the fluorescent measurement of quinidine.*

*There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Thiazides and triamterene cross the placental barrier and appear in cord blood. The use of thiazides in pregnancy requires weighing the anticipated benefit against possible hazards, including fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Thiazides appear, and triamterene may appear, in breast milk. If use of the drug is essential, the patient should stop nursing. Safety and effectiveness in children have not been established.*

***Adverse Reactions:*** *The serious adverse effects associated with 'Dyazide' have commonly occurred in less than 0.1% of patients treated with this product. Anaphylaxis, rash, urticaria, photosensitivity, cardiac arrhythmias, postural hypotension, diabetes mellitus, hyperkalemia, hyperglycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia, jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain, acute renal failure, interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment, leukopenia, thrombocytopenia and purpura, megaloblastic anemia, muscle cramps, weakness, fatigue, dizziness, headache, dry mouth, impotence, sialadenitis. Thiazides alone have been shown to cause the following additional adverse reactions: paresthesias, vertigo, xanthopsia, transient blurred vision, allergic pneumonitis, pulmonary edema, respiratory distress, necrotizing vasculitis, exacerbation of lupus, aplastic anemia, agranulocytosis, hemolytic anemia. In neonates and infants: thrombocytopenia and pancreatitis—rarely, in newborns whose mothers have received thiazides during pregnancy.*

***Supplied:*** *Capsules containing 25 mg hydrochlorothiazide and 50 mg triamterene, in bottles of 1000 capsules; in Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.*

*BRS-DZ:L59*
*a product of*
**SK&F LAB CO.**
*Cidra, P.R. 00639*
*© SK&F Lab Co., 1989*

Journal of the Arizona Medical Association

ARIZONA MEDICINE

April 1990, VOL XLVII, No. 4

Marshall B. Block, M.D.

# The Wisdom of Common Sense

An elderly patient who presented with a breast mass subsequently had a mammogram which showed a lesion which was suspicious for an underlying carcinoma. Prompted by a daughter living "Back East" who had a similar problem several years earlier, the patient traveled to one of the world's meccas for breast surgery. There she was seen in consultation by a "world famous" surgeon. He suggested a modified radical mastectomy to the patient in order to "cure" her disease. The patient being 80 years of age and of sound mind responded by stating, " I think I am going to die of old age before I am going to die of this breast lesion! Could we not just remove the lump and leave the breast?" After much discussion and multiple attempts to cajole the patient, the surgeon reluctantly agreed to do a lumpectomy. The patient returned home with two breasts, minus one lump, but promised to have radiation therapy at a facility far from her home to appease the attending surgeon who knew of only one radiation therapist in her state. I called one day to see how she was doing and her husband answered the phone. He stated that he had a new job. I was a bit surprised and asked him what this entailed and he replied, "I'm a taxi driver! I drive her sixty miles each way for her radiation therapy!" I chuckled and he continued, "You know, they're rich in this community, you can tell by the way they dress!" I chuckled again and he continued, "It makes no difference though, they got the same diseases the rest of us have!"

The simplicity of "common sense" needs to be invoked many times in our daily practices. For instance, when a patient with Alzheimer's disease and hyperparathyroidism presents, might not surgery for her mild hypercalcemia be withheld? Does mild anemia and positive stools in a 93-year-old woman require an extensive evaluation searching for a malignancy? Should we consider dialysis in a 95-year-old man with progressive renal insufficiency? All of these situations are real and have occurred in my practice in the last month. Where does "common sense" enter into the equation? Who should be the one making the decisions in these types of situations?

We in our lifetime have seen the transformation of medical therapy for many diseases. What today seems like established dogma, tomorrow is decidedly different. From radical mastectomy to lumpectomy, from 100 units Regular Insulin IV push to 5 units IV drip per hour, for diabetic ketoacidosis, from coronary artery bypass surgery to angioplasty, dramatic changes in the treatment of medical problems have occurred without apparent significant differences in morbidity or mortality. There is so little that we know for sure, but much that we are expected to support wholeheartedly. The expectations of our patients and our own self worth are dependent upon us making the right decisions when in fact these decisions are often mere guesses. A healthy and happy balance needs to be reached regarding intellectual honesty and the need to be authoritarian, both for our patient's benefit and our own. We must continue to walk this difficult ground between giving patients confidence in our ability to heal them, yet being honest enough to recognize the softness of our knowledge. As my patient's husband inferred, disease knows no barrier nor does the search for truth. We must keep that in mind every time we enter the examining room (nee, the Twilight Zone).

**Marshall B. Block, M.D., Editor**

Journal of the Arizona Medical Association

ARIZONA MEDICINE

April 1990, VOL. XLVII, No. 4

*Arizona Medicine* is a socioeconomic and scientific journal published monthly by the Arizona Medical Association, Inc., 810 West Bethany Home Road, Phoenix, Arizona 85013, in conjunction with *The Western Journal of Medicine*. All views and opinions expressed in the articles published herein are the authors' and may or may not reflect those endorsed by the Arizona Medical Association.

(602) 246-8901 in Phoenix
1-800-482-3480 Statewide

Mark Ivey, Jr. M.D.
*President*

Chic Older
*Executive Vice President*

Marshall B. Block, M.D.
*Editor*

Susan Fuchs
*Director of Communications*

Gayle Mueller
*Publishing Coordinator*

Linda N. Brown
*Editorial Assistant*

Please notify publisher at least six weeks prior to change of address and include old and new addresses and a mailing label from most recent copy of *Arizona Medicine*. Include your new postal Zip Code number.

## In This Issue:

- The Changing Nutritional Smorgasboard: Issues for the 1990s
- Special Service Codes
- Gross Revenue Protection for Self-employed Physicians
- Letter to the Editor
- Gleanings from ArMA Past
- Physicians in the News
- Personal Productivity
- Children and Backyard Swimming Pools
- New Members
- Classified Ads

# From Our President

**Mark Ivey, Jr., M.D.**
**President, ArMA**

We are engaged in a struggle for which we will be held accountable by the generations to come. We all have a stake in the outcome of the struggle; we are all responsible for the future of medical care in America.

During the first months of World War I, generals were handling large armies under unprecedented circumstances. The Germans were halted on the western front as a result of the Battle of the Marne, the battle that saved France from defeat. Marshal Joffre was in control of the French Army.

Years later military generals would debate and discuss who really should have credit for the victory. Surely some general made some move at exactly the right time in precisely the right direction with no question as to the brilliance of the move. There was disagreement; opinions varied and finally the question was put to Marshal Joffre himself.

After contemplating the battle for a few minutes, he said, "I really don't know who ought to get the credit for the victory at the Marne. I know only one thing. If we had been defeated, everyone would have agreed at once that the fault was mine!"

The retrospectoscope has been, and always will be, an excellent instrument for determining what went wrong. But we need leaders with vision and courage and a will to help individual patients who can not be detoured by self-serving special interest groups.

I am convinced that strong leadership can look inward and find answers that will cause our practice of medicine to excel beyond our wildest imaginations. They say when you speak to others for their own good, it's advice; when they speak to you for your own good, it's interference.

All of us are trying very hard to understand what it is that the federal government is trying to say to us. Unfortunately, we are in a battle that not only has major proportions of interference, but probably has designs on our patients' futures that we are not privy to. In this profession, however, we know our potential and our limits and the importance of perseverance, no matter what kind of interference we face.

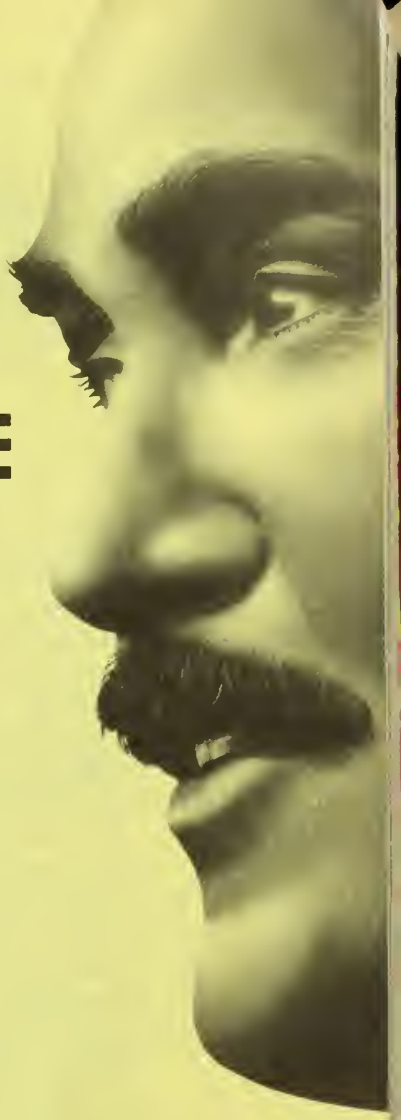
In spite of the challenges thrown into our path by the politicians and bureaucrats, we must remember that as physicians, we are patient advocates. We are not agents of the government, especially when the government is more concerned about the health of its budget than the health of its citizens.

We are not gatekeepers, even though we've mended a lot of fences. We are not providers, although we've given away much of the medical profession. First and always, we are physicians who care, physicians who put the patient first.

**Mark Ivey Jr., M.D.**

Recently, MICA conducted a survey of our policyholders to discover what questions they had about medical malpractice insurance. During the next few months, we'll respond to their questions.

# COMMONLY ASKED QUESTIONS ABOUT MEDICAL MALPRACTICE INSURANCE ANSWERED BY MICA



**What factors cause rates to increase or decrease?**

The frequency and severity of claims are major factors influencing rates. Other factors include inflation, increasing health care costs, expansion of liability doctrines, and judicial activism. MICA's operating expenses (among the lowest in the industry) and investment income also influence rates.

**How are reserves invested?**

State statutes regulate and prescribe the manner in which insurance company funds can be invested. For example, no more than 10% of assets can be invested in any one company, and no more than 20% of assets can be invested in common stocks.

Within these parameters, the MICA Investment Committee directs the management of the company's assets in an effort to keep policyholders' rates down. The committee's mission is to pursue prudent growth, mindful of tax considerations and liquidity requirements.

The portfolio of investments includes Municipal Bonds, US Treasury Bills, and Common Stock in the most appropriate combination. Our results have been consistently successful.

**How is MICA's Board of Directors elected and compensated?**

All thirteen of our Board members are physicians. These trustees are nominated by committee and their names are disseminated to the membership. Once elected they serve a one year term.

Board members are compensated at the rate of $90 per hour for attending meetings and working on committees. In addition they receive travel compensation.

MICA hopes the answers to these commonly asked questions will help physicians better understand the complexities of medical malpractice insurance.

As a doctor-owned malpractice carrier – insuring more Arizona physicians than any other company – MICA's mission is to provide professional insurance at the lowest actuarially sound rates.

**MICA Mutual Insurance Company of Arizona**

To learn more call MICA: **(602) 956-5276** or Toll Free **(800) 352-0402.**

# The Changing Nutritional Smorgasbord: Issues For the 1990s

In the 1970s and early 80s, interest among medical educators and nutritionists turned to the need to develop and integrate nutrition in medical school curricula. This attention was at least in part due to studies which showed that hospitalization is a potent risk factor for malnutrition. Research developments during this era led to new methods of nutritional support, revolutionizing the treatment of some conditions and the management and survival of very low birthweight newborns. By the mid to late 1980s, our knowledge of human nutrient requirements had advanced considerably, as had the epidemiological and clinical databases linking diet and risk of chronic disease. As we begin the 1990s, the value of nutritional support in acutely ill patients is taken for granted. The effectiveness of dietary changes in reducing risk of cancer, heart disease and osteoporosis is still under study, but is increasingly accepted as desirable not only by the medical community but also by the public.

Yet there are major unsolved problems, and the 90s will bring new challenges. Among them:

Cost-containment means shorter hospital stays and the management of sicker patients at home and other settings; it also means home total parenteral and enteral nutrition, long-term nutritional support for geriatric and chronically ill patients, and teaching which focuses on applying available nutritional knowledge and technology outside the hospital setting.

Implementing dietary recommendations designed to reduce the risk of chronic disease will pose challenges of effectiveness and cost of patient education; for example, the National Cholesterol Education Program's recommendations provide for dietary counseling for fully one-fourth of adults screened for hypercholesterolemia.

Research into the etiology of diet-related disease will continue to be a major focus of effort, particularly in relation to cancer.

The appearance on the scene of AIDS is making major changes in the medical care and public health worlds. The very definition of the disease implies malnutrition, and its spread creates new challenges for nutritional support. In Africa, the spread of AIDS has ominous consequences for the health and nutrition of children as well as adults; not only are children affected with the disease through vertical transmission, but those orphaned by the disease are put at high risk of malnutrition and death. The cost of fighting AIDS will have major impacts on the availability of preventive services, including nutrition services, in countries with limited resources.

Almost half of children and many adults in developing countries continue to suffer from overt nutrient deficiencies, and the nutritional situation in many countries of Africa and Latin America has actually worsened in the last several years. In addition, demographic shifts in the third world mean that many countries must begin to face problems of aging populations in resource-poor environments, and must tackle the nutritional aspects of geriatrics and of chronic disease at the same time that they still suffer from endemic malnutrition among children. An international perspective on clinical and public health nutrition will be essential for the 1990s and beyond; we cannot afford to educate physicians who are ignorant of preventable and treatable conditions which afflict millions of people worldwide.

From The University of Arizona, Tucson, 85724. Dr. Harrison is Professor of Family and Community Medicine, Acting Dean of the Graduate College and Assistant Vice President for Research.

**Gail G. Harrison, Ph.D.**

# PUT YOUR MEDICAL CAREER IN FLIGHT.

Discover the thrill of flying, the end of office overhead and the enjoyment of a general practice as an Air Force flight surgeon. Talk to an Air Force medical program manager about the tremendous benefits of being an Air Force medical officer:

- Quality lifestyle, quality practice
- 30 days vacation with pay per year
- Support of skilled professionals
- Non-contributing retirement plan if qualified

Discover how to take flight as an Air Force flight surgeon. Talk to the Air Force medical team today. Call

USAF Health Professions
Toll Free
1-800-423-USAF

AIR FORCE

# Special Service Codes

## Introduction

Are you spending time seeing patients on an emergency basis or after hours? Did you know that there are special service codes available just for those occasions?

In the following paragraphs we will discuss the CPT-4 special service codes and how using them will help you code accurately and ensure optimum reimbursement for your services.

## Identifying Special Service Codes

Special service codes are an adjunct to the physician's basic service. Use of these codes depends on the circumstance surrounding the basic service. There are approximately 44 special service codes available in the 1990 CPT-4 book and can be found on pages 60-64. Special service codes are easily identified because they begin with "99." For example, the special service code for "Services Requested After Hours" is 99050. Special service codes are designed for all medical specialties. Some specialties may use these codes more often than other specialties. For example, a cardiologist may tend to see more patients after office hours or on an emergency basis than a urologist.

## SPECIAL SERVICE CODES Partial List

The following examples illustrate the correct way in which to use special service codes as an adjunct to the basic service.

*Example #1*

99050 - Service requested after office hours in addition to the basic service.

Example of use: 90050 - Established patient, limited — +

99050 - Service requested after hours (6:30 p.m.)

Documentation: To submit a clean claim, be sure that the time of the visit is documented on the claim form. Also, be sure that the time and any special circumstance pertaining to the patient's after hours visit is documented in the patient's chart. It is always a good idea to inform the patient of the additional charge for an after hours visit prior to the scheduled time.

*Example #2*

99058 - Office services provided on an emergency basis.

Example of Use: 90050 - Established patient, limited — +

99058 - Office service provided on emergency basis

Documentation: To submit a clean claim, be sure that the diagnosis supports the use of the emergency special service code. For example, a laceration, broken bone or foreign body in the eye may constitute an office service provided on an emergency basis. Also, be sure that the emergency circumstance is documented in the patient's chart.

99100 - Anesthesia for patient of extreme age, under one year and over 70.

Example of Use: 01464 - Anesthesia for arthroscopic procedures of ankle joint — +

99100 - Anesthesia for patient over 70

Documentation: Since modifiers may not be appropriate in this situation, use of the special service code may better describe the special circumstance. Be sure to document the special circumstance in the patient's chart and in the anesthesia report.

## Reimbursement for Special Service Codes

Reimbursement for special service codes varies among insurance carriers. However, this variation should not deter you from using these codes. Medicare, for example, may allow up to $13 for the special service code 99052-(Services Requested Between 10:00 p.m. and 8:00 a.m.) in addition to the basic service. If handled properly, charging the patient for special service codes should not create "superbill shock." That is why we always recommend establishing standard billing and collection procedures for these services.

## Summary

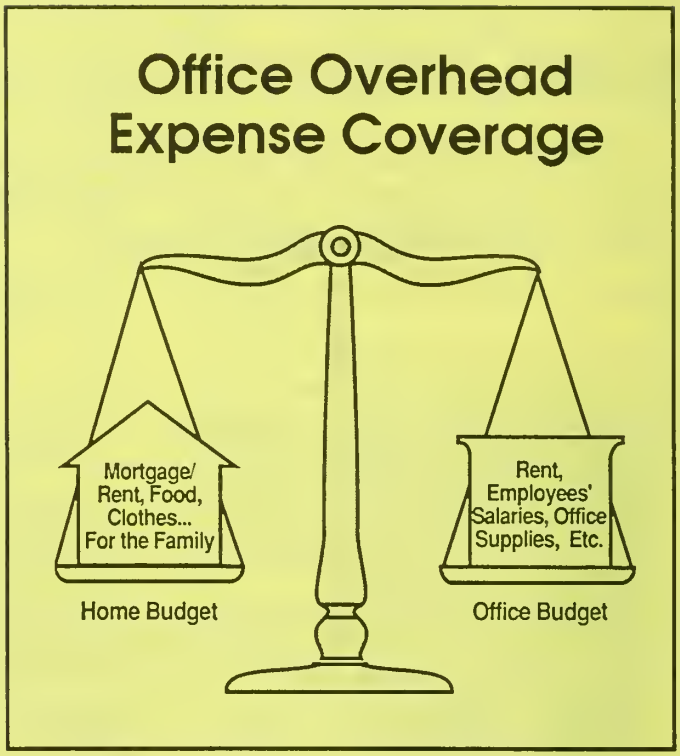
While special service codes are appropriate when circumstances warrant their use, the physician must always document the special circumstance in the patient's chart for future reference. Since special service codes are used as an adjunct to the basic service, establishing reasonable charges for special services is recommended. Remember, the patient is directly affected, so be sure that standard billing and collection policies are in force prior to using the codes.

*Claire Miller and Joan Miller are President and Chief Financial Officer of SysteMedical Management, Inc., a medical practice management firm located in Mesa, Arizona. They can be reached at (602) 833-4855.*

**Several key Medicare reimbursement and policy changes will be phased in within the next several months, starting April 1. Here is the timetable for implementing these changes:**

| EFFECTIVE DATE | PROVISIONS |
|---|---|
| April 1, 1990 | Medicare fees are updated for 1990 and decisions for March participating/non-participating sign-up become effective. |
| April 1, 1990 | Physicians must accept assignment for all Medicare patients that are also eligible for Medicaid benefits. |
| April 1, 1990 | Payments are reduced for "over-valued" services, radiology services and anesthesia services. |
| April, 1990 | Unassigned claims that fail to include ICD-9 codes will be referred to HHS Inspector General for possible sanctions. |
| May, 1990 | Assigned claims that do not include Medicare carrier identification numbers of the performing physician will be rejected. |
| July, 1990 | Assigned claims will be denied if ICD-9 codes are incomplete or inaccurate. Unassigned claims will be referred to the HHS Inspector General for failure to submit complete or accurate ICD-9 codes. |
| September, 1990 | Physicians must submit all Medicare claims to carriers regardless of the assignment decision. |
| September 1, 1990 | Medicare carriers will initiate Congressional mandate to profile individual physicians whose practice patterns vary significantly from peer group norma. This activity should not be punitive, but, rather an educational effort to advise physicians of practice variations. |
| October, 1990 | HCFA to begin implementing phase-out of local codes. Impact will vary and be limited to a handful of states. |

# Gross Revenue Protection for Self-Employed Physicians



Rick Sechler, ArMA
Membership Benefits

"Double jeopardy" is a useful term to describe the dual responsibilities faced by the self-employed physician. As depicted by the accompanying illustration, both the home budget and the office budget must be funded, even if an accident or injury prevents or inhibits the ability to practice medicine. To insure one without insuring the other is self-defeating. If personal disability income dollars are used to fund office expenses, the family will suffer. Office overhead expense benefits can only be used for reimbursable, itemized business expenses, *not* for personal expenses. Therefore, owning one coverage without the other puts both budgets in jeopardy.

Personal expenses such as mortgage payments, food, clothing, education and entertainment will continue even though the family provider may become disabled. Personal disability income protection, preferably issued on a specialty-specific basis, is the solution.

The expense of continuing the practice until recovery or sale is also ongoing. Lease payments, employee salaries, and malpractice premiums will continue and are usually contractually necessary to keep the doors open until other arrangements can be made. Business Overhead Expense (BOE) coverage will allow you to fund these obligations without eroding your personal disability benefits.

The professional advisors from ArMA Financial Services and Membership Benefits can help you evaluate your current protection and arrange for additional coverage. Call Rick Sechler at 246-8986 or 1-800-482-3480 for additional information and a review of your situation. This review is a benefit of your ArMA Membership and is provided without cost or obligation. ■

## Gleanings From ArMA Past

Those Who Went Before

Howard Currie James, M.D.
1906-1960

After special training in obstetrics, he arrived in Tucson in 1935. He served in many capacities in local medical and staff positions.

A fellow practitioner summarized Dr. James' life and devotion to work: "Dr. James delivered over six-thousand babies and there were no maternal deaths. This high standard of personal and professional response to the practice of medicine is a final salute to a great doctor."

Fredrick Valles, M.D.

"Doctor Valles was born in Tacna, Peru and received his undergraduate education in Spain, and medical degree from the University of San Marcos, Lima, Peru, in 1907.

Although devoted to medicine, his restless mind would not remain in this ivory citadel. He expressed himself elegantly as a humanitarian, a poet, a philosopher, a scientist and a world traveler.

Much of his poetry, essays and scientific contributions were published in Spanish, Italian, French and Portuguese periodicals; thus they have eluded the English press.

He practiced in Argentina first, and arrived in Tucson in 1921 and practiced there until his death. He saw and partook of a new frontier of science, humanity and intellectualism." So wrote Doctor Edwin A. Busse, of his colleague.

**Dry Gulch Jake**

# To the Editor:

*Dear Sir:*

*It is a proper function of the editorial writer to call attention to potentially unhealthy trends and concepts.*

*Part of our essay on stress is illustrated by the agitation of one reader. Whenever a reaction seems out of all proportion to a stressful provocation, then it becomes necessary to identify seemingly unrelated physical and mental vulnerabilities and especially the underlying personality type.*

*Abstracting, we create such monsters as stress and then react to them as if they were real. We speak of the stress of a debilitating illness, for example. No; only one entity is involved, not two. The stress is the illness; the illness is the stress and they cannot be separated.*

*The fallacy is reification; i.e., treating an abstraction as if it had concrete reality. Widespread failure to recognize this fallacy is a hindrance to progress in science, in philosophy, in politics and in all branches of learning.*

*Yours very truly,*
***William B. McGrath, M.D.***


**Allergy and Pregnancy Seminar**
**May 11, 12, 13, 1990**
The Registry Resort
7171 North Scottsdale Road
Scottsdale, Arizona 85253

Program Director: Merle S. Scherr, M.D.
Co-sponsored by the Greater Phoenix Allergy Society
The Arizona Allergy Society
Scottsdale Memorial Hospital, Department of OB/GYN
Arizona Perinatal Society
Allergy and Pregnancy Committee of
American College of Allergy and Immunology
For further information, please call Merle S. Scherr, M.D.
(602) 994-9514

# Physicians in the News

Several Arizona doctors are among a group of 900 physicians throughout the United States participating in a medical study to evaluate the effects of a new antihypertensive drug.

Local physicians involved in the study include:

**Katherine E. Dickinson, M.D.,** Safford

**Ian G. Becke, M.D.,** Cottonwood

The purpose of the study is to try to determine what affect, if any, the drug, Carteolol, has on cholesterol and triglycerides. Carteolol has already been approved by the FDA for lowering high blood pressure.

Participating physicians offer patients who are either not taking medication for high blood pressure or who are taking medication which is not effectively controlling the problem the option of getting involved in the study. It is hoped each physician will be able to involve 25 patients in the study.

According to the requirements of the study, the participating patients are not suppose to be on Medicare, AHCCCS or any other federal funding for their care.

The study, sponsored by the Tulane University School of Medicine through an educational grant from Abbott Laboratories, is the first known study involving community physicians transmitting results to a major medical institution using lap top computers. Participating physicians received lap top computers in September. They record the data on disks and mail them to the University where the information is entered into the database.

The program is expected to involve up to 25,000 patients in the year-long study with updates and final results available to the medical community nationwide via Tulane's database.

Katherine Dickinson, M.D., has been a family practitioner in Safford for one and one-half years. She graduated from George Washington Medical School and completed her residency at the University of Arizona.

Ian Becke, M.D. has actively practiced internal medicine in Cottonwood for the past 10 years. He graduated from the University of Sydney, Australia, and trained at Columbia Presbyterian in New York.

**Richard H. Reznick, M.D.,** a Scottsdale pediatrician, has been elected Chief of Staff at Phoenix Children's Hospital.

As Chief of Staff he represents the 700-physician medical staff interfacing with administration. He feels communication between the two is good and that the Board of Directors is very responsive to medical staff concerns. The desire of both is to make PCH the best in the community.

**Richard H. Reznick, M.D.**

One of his goals as Chief of Staff is to inform the community at large of the availability of pediatric services for children. He also wants PCH to have its own facility in conjunction with an existing medical center, and thus be able to provide a wider range of pediatric and other services.

Dr. Reznick, who moved to Arizona from Chicago in 1971, has been actively involved with PCH for many years. he served as chairman of a number of committees including credentials committee, public relations-advertising committee, and bylaws committee and was Vice Chief of Staff from 1983-1985. ■

# WHITE WATER

**$79** Per person plus tax

10 miles with lunch. Great idea for family, staff, and clients.

**461-9494**

***SALT RIVER CANYON WHITE WATER RAFTING***

# MEDICAL BOOKSTORE

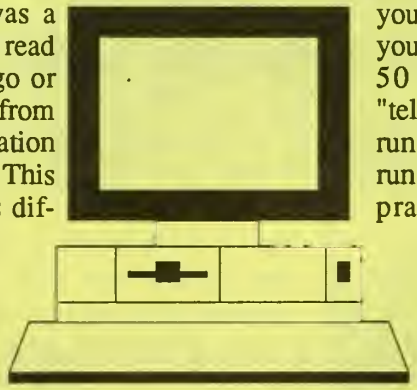
**MEDICAL BOOKSTORE**
College of Medicine
Arizona Health Sciences Center
Tucson, Arizona 85724
Phone: 626-6669

None of these go unanswered when you lease your vehicle through **ArMA's** new vehicle leasing program. Call your **ArMA** vehicle benefits representative, ***RC Auto Corporation (602) 249-3951.***

*The new information utilities can retrieve by searching for a single word.*

# Personal Productivity

Ok, you've got the four basic software groups covered. You're typing letters on word processing, tracking patients with the database, doing "whatif" scenarios on the spreadsheet and posting it all to some unknown place with the communications package. Then how come when it comes time to find just a single piece of information you need, none of these packages seem to help? Perhaps it was a journal article that you read a couple of months ago or you need that name from the curbstone consultation you had just last week. This kind of information is difficult to track with any of the four basic software groups. It is best tracked with a little known, often misunderstood form of software called "utilities." Most people relate software utilities to doing housecleaning tasks of computer maintenance. While this is true, the latest utilities can be made to work in much the same way as the human memory, that is, one word can trigger the information that you need on the fly without tracking it or looking it up in a database. There are many different kinds of "utilities," The ones we will look at today deal specifically with information retrieval.



The *"Memory-Mate"* program by Broderbund is one of the best. This free form utility allows the user to simply input the information. It doesn't care if it is on a new page or attached to some other info. It only has 15 commands and the user really only uses about five. If you put in a name and phone number that is what it will remember. The same holds true for any kind of information, meeting dates, *(the program is date sensitive and will remind you)*. In short, anything you type into the program is remembered. But now comes the good part! You as the user need only remember "one word" to recall that information. The program will search itself and return to you those entries which have that "one word." Additionally, after the program finds all the information it will allow you to "narrow" your search so you don't have to look under 50 entries for, let's say "telephone." This package will run memory resident so it can run underneath your existing practice software or word processor and can be recalled with just a one key command. The program also will allow you to keep many different kinds of data. This is akin to keeping random information in 50 gallon drums. You can dedicate a 50 gallon drum for journals, another for personal, and another for prescriptions and so on. It will also enable you to *hypertext* information, which allows you to electronically tie the information together. A package like this costs about 40 bucks in the software stores and can be learned soup to nuts in about an hour. Hardly a major investment and when it returns your request in two seconds a smile will come to face. This is the stuff computers were meant to do.

**Thomas Marks**
**Director, Management Information Services**

**JUST BECAUSE IT'S LEGAL DOESN'T MEAN IT'S SAFE.**

Alcohol and some medications can cause serious birth defects. Call your Association for Retarded Citizens for more information.

arc
Association for Retarded Citizens

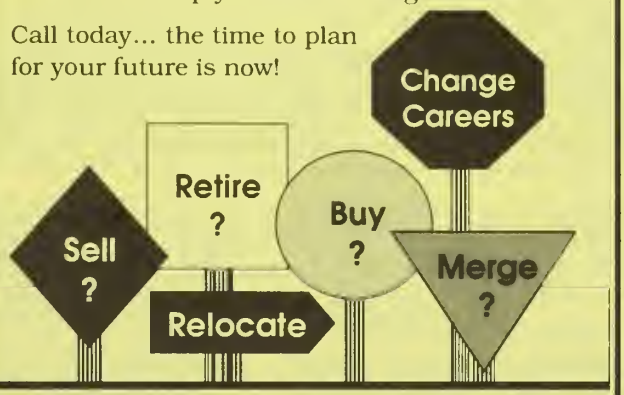


## *WHAT SHOULD I DO NEXT?*

Not sure? Let us help determine your needs, explore your options, and design a program that will maximize your "Quality of Life"... NOW.

No matter how far along you are in your career, AFTCO can help you make the right move.

Call today... the time to plan for your future is now!




"EQUITABLE TRANSACTIONS THROUGH DUAL REPRESENTATION"

**Aftco® Associates**

3636 N. CENTRAL AVENUE, STE. 820
PHOENIX, AZ 85012
— (602) 222-4141 —

*ESTABLISHED 1968 • OFFICES LOCATED NATIONWIDE*

PRACTICE SALES/MERGERS | PRACTICE APPRAISALS | RELOCATIONS
EQUITY ASSOCIATESHIPS | CONTRACT SERVICES | CAREER TRANSITIONS


## ARIZONA PHYSICIANS' DIRECTORY

**MOVING YOUR PRACTICE?**
**ANNOUNCING AN ASSOCIATE?**
**SATELLITE OFFICE? — NEW PRACTICE?**

Block space is available in ***Arizona Medicine*** in 1/4 page blocks—Two-month minimum—$20.00 per month for member physicians — $30.00 per month for non-members. Please notify the Publications Department by the 1st of the preceding month of publication. Typesetting will be provided at no extra charge.

# Children and Backyard Swimming Pools

*(Editor's Note:*
*The following policy statement was developed and approved by the Arizona Chapter of the American Academy of Pediatrics. Its message should be shared with all parents or other relatives whose families include toddlers and backyard swimming pools.)*

From 1980 - 1985, 229 children less than 14 years of age died as a result of drowning in Arizona. 165 of these Arizona children were between the ages of one and four. Nationally, drowning is the second leading cause of unintentional death in the home to children under five years of age. In many states, i.e., Arizona, California, Florida and Texas, it has been the number one cause. Approximately 80% of these Arizona deaths occurred in backyard swimming pools.

Arizona (particularly Maricopa and Pima Counties) has one of the highest ratios of pools to private residences in the country. This ratio may be as high as one in four, with recent studies showing total numbers of backyard swimming pools to be 125,000 in Maricopa County alone. In Maricopa County there are about 17,000 backyard pools in private residences with children less than five also living at that residence. In the first ten months of 1989, 27 children less than five years of age drowned.

In addition, there are a large number of children who survive near drowning events. Emergency rooms, police or fire departments report at least five near drownings for each reported death. Data for Maricopa County suggests up to 7% of pool owners recall at least one near drowning episode in their pool. The majority (83%) of these were with young children. Many near drowning victims suffer irreparable brain damage with later devastating financial and emotional costs to their families and communities. Medical costs for initial hospitalization alone average $20,000 for a fully recovered victim, and $80 - 150,000 for a child with severe brain damage.

Many public and private strategies have tried to decrease these rates. Pima and Maricopa Counties have developed aggressive public awareness programs. There remains no proven single effective method of prevention.

### Statement

Childhood drowning is preventable. Parents must recognize and accept the risk associated with any body of water, including the backyard pool. *The surest way for parents to prevent drowning of children less than five years of age is not to have a backyard swimming pool.* If a pool is present, parental responsibility must include both active and consistent behavioral changes and intensive implementation of passive barriers to prevent their child from drowning.

### Necessary Active and Consistent Behavioral Changes:

1. Admit that no child is "water safe," even if the child knows how to swim.
2. Provide constant eye contact supervision to include designated adult "lifeguards" whenever children are in the pool.
3. Keep the pool area clear of toys.
4. Do not permit children to use inflatable toys and mattresses as life preservers.
5. Install a fixed phone near the pool. Keep emergency numbers with the phone.
6. When seeking child care (i.e., babysitters), whether in or out of the home, consistent behaviors regarding pool activity and access must be maintained and guaranteed by parents.
7. Educate children regarding safety rules and reinforce them during swimming.
8. Consider temporary filling of the pool with dirt or sand.
9. Infant swim programs or water adjustment programs should be understood by parents to be of unproven value in prevention of childhood drowning. It is unlikely that infants can be made "water safe." The parents of these infants may develop a false sense of security if they believe their infant can "swim" a few strokes.
10. Learning CPR (cardio-pulmonary resuscitation) may prevent death from a submersion injury. Although CPR training cannot be considered a primary preventive behavior, parents who have accepted the risk of a backyard pool must be ready to act in

an emergency and should be CPR trained. CPR training should be completed by any adult who provides supervision, such as grandparents, babysitters, lifeguards, etc.

**Necessary Passive Barriers to be implemented by pool owners:**

1. Pool isolation fencing should be installed. A permanently installed isolation fence should be placed between the home and the pool. If properly installed, the barrier should serve as a deterrent, being difficult for a child under five to climb over, under or pass through. The barrier should not restrict a clear view of the pool from the house. This barrier is only effective if it is in good repair and kept securely closed and locked when a supervising adult is not physically present.
2. The next layer of protection between a child and the pool is to secure all windows and doors leading to the yard. Self-closing and self-latching doors and windows can be installed to prevent unobserved access to the yard.
3. Pool alarms and pool safety covers add additional layers of protection, however, they do not replace necessary behavior changes nor the installation of a permanent isolation barrier as described above.

***The younger the child, the greater the number of active behavioral changes and passive barriers are necessary. Any one behavior or barrier alone will not prevent childhood drowning.*** ■

## AMA Conference to Explore Testing, Counseling, and Care of HIV Patients

The American Medical Associaiton will sponsor its second annual "AMA HIV Conference: Counseling, Testing and Early Care," June 18-19, 1990, at the Westin St. Francis Hotel, San Francisco, California. The AMA conference will precede this year's international AIDS conference, also taking place in San Francisco.

Topics to be covered at the AMA conference include:

- An overview of early care, what should be done; what isn't.
- The special needs of special populations, including infants and women, blacks and hispanics and IV drug users.
- Perspectives from HIV-infected physicians.

Among the invited featured speakers: Paul Volberding, M.D., San Francisco General Hospital, Samuel Perry, M.D., Cornell Medical Center, Karen Hein, M.D., Montefiore Medical Center and Gary Noble, M.D., Centers for Disease Control.

Those wishing future registration or program information should contact AMA Registration Services, 535 N. Dearborn, Chicago, Illinois, 60610.


Arizona Medical Association

99th Annual Meeting

June 7, 8 & 9

Wyndham Paradise Valley Resort

Scottsdale

# New Members

*The Arizona Medical Association welcomes the following new members:*

## *Active*

### Coconino

**Henry W. Poore, M.D.**
Family Practice
General Surgery
Rt. 4, Box 980, Flagstaff
University of Virginia
School of Medicine
Charlottesville - 1957

**John R. Steenbarger, M.D.**
Pediatrics
Neonatal-Perinatal Medicine
77 W. Forest Avenue, #204
Flagstaff
University of Nebraska
College of Medicine - 1974

### Gila

**Mark M. Garskof, M.D.**
Family Practice
703 Ash Street, Globe
State University of New York
Stony Brook School of Medicine - 1975

### Maricopa

**John W. Bass, M.D.**
Plastic Surgery
2218 N. 3rd Street, Phoenix
University of Missouri
Kansas City School of Medicine - 1982

**Albert L. Boyd, M.D.**
Family Practice
13200 N. 103rd Avenue, #34
Sun City
University of Michigan
Medical School - 1961

**William K. Brubaker, M.D.**
Internal Medicine
2807 N. 11th Avenue, Phoenix
University of Arizona
College of Medicine - 1981

**Peter M. Burkholder, M.D.**
Pathology
P.O. Box 5099
Department of Pathology
Phoenix
Cornell University
Medical College - 1959

**Alan Y.M. Chang, M.D.**
Pediatrics
P.O. Box 11000, Mesa
Medical College of
Wisconsin, Milwaukee - 1973

**Jimmy E. Chevalier, M.D.**
Allergy
Pediatrics
5410 W. Thunderbird, #200
Glendale
University of Texas Medical
School, San Antonio - 1976

**H. Royer Collins, M.D.**
Orthopedic Surgery
3320 N. 2nd Street, Phoenix
University of Rochester
School of Medicine & Dentistry - 1957

**Wolfgang F. Dahnert, M.D.**
Radiology
1111 E. McDowell Road, Phoenix
Faculty of Medicine
Gutenberg University - 1976

**Drake D. Duane, M.D.**
Neurology
10250 N. 92nd Street, #117
Scottsdale
Wayne State University
School of Medicine, Detroit - 1962

**Bruce E. Freedman, M.D.**
General Surgery
515 W. Buckeye Road, #401
Phoenix
University of Arizona
College of Medicine - 1982

**Robert F. Guyette, M.D.**
Maxillofacial Surgery
Plastic Surgery
3501 N. Scottsdale Road
Scottsdale
University of Alabama
School of Medicine - 1987

**Jeffrey H. Hill, M.D.**
Pediatrics
Pediatric Critical Care
350 W. Thomas Road, Phoenix
University of Chicago
Pritzker School of Medicine - 1978

**Thomas J. Ketterer, M.D.**
Otorhinolaryngology
560 W. Brown Road, #1008
Mesa
State University of New York
College of Medicine, Syracuse - 1984

**Alberta L. Mazzei, M.D.**
Anesthesiology
P.O. Box 5099
Department of Anesthesiology
Phoenix
University of Pennsylvania
School of Medicine - 1985

**Robert R. McCulloch, M.D.**
Ophthalmology
11209 N. Tatum Blvd., #250
Phoenix
Creighton University
School of Medicine - 1983

**Mark A. Meyers, M.D.**
Dermatology
4045 E. Bell Road, #125
Phoenix
Chicago Medical School - 1974

**J. Phillip Nelson, M.D.**
Orthopedic Surgery
13400 E. Shea Blvd.,
Scottsdale
Northwestern University
Medical School - 1962

**Vincent J. Nicchi Jr., M.D.**
Cardiovascular Diseases
Internal Medicine
13200 N. 103rd Ave., #31
Sun City
Universidad Del Noreste,
Tamaulipas - 1981

**Jay J. Rozaci, M.D.**
General Surgery
Vascular Surgery
215 S. Power Road, #A-201, Mesa
Charles University
Faculty of Hygiene, Praha - 1974
**David L. Simms, M.D.**
Otorhinolaryngology
3326 N. 3rd Avenue
Phoenix
University of Oklahoma
College of Medicine - 1984
**Juan M. Tellez, M.D.**
Anesthesiology
6424 E. Broadway, #102, Mesa
Baylor College of Medicine - 1985
**Pierre R. Tibi, M.D.**
Cardiovascular Surgery
Thoracic Surgery
1300 N. 12th Street, #508
Phoenix
University of Pittsburgh
School of Medicine - 1982
**Glenn K. Yarbrough, M.D.**
Dermatology
3302 N. Miller Rd., #D
Scottsdale
Texas Tech University School
of Medicine, Lubbock - 1982

## Pima

**Mark S. Bessette, M.D.**
Family Practice
6566 E. Carondelet Dr.
Tucson
University of Minnesota
Medical School, Minneapolis - 1986
**Deborah M.S. Blattstein, M.D.**
Obstetrics & Gynecology
Arizona Health Sciences Center
Department of OB/GYN
Tucson
Baylor College of Medicine - 1984
**Randall C. Cork, M.D.**
Anesthesiology
Arizona Health Sciences Center
Anesthesiology 5319
Tucson
University of Arizona
College of Medicine - 1977
**Veronica J. O. Gaetze, M.D.**
Obstetrics & Gynecology
1980 W. Hospital Dr., #100
Tucson
University of Missouri
Columbia School of Medicine - 1976
**Charles S. Kaplan, M.D.**
Internal Medicine
Infectious Disease
6565 E. Carondelet Drive
Tucson
Tufts University
School of Medicine - 1984
**Neil R. West, M.D.**
Pediatrics
P.O. Box 40550, Tucson
Baylor College of Medicine - 1966

## *Associate*

## Maricopa

**Loren E. Imes, M.D.**
Internal Medicine
12507 Eveningside Dr.
Sun City West
University of Nebraska
College of Medicine - 1942

## *Resident*

## Maricopa

**James T. Canavan, M.D.**
Anesthesiology
P.O. Box 5099
Department of Anesthesiology
Phoenix
University of Oklahoma
College of Medicine - 1987
**Michael E. Clevenger, M.D.**
Neurology
350 W. Thomas Road
Phoenix
University of Oklahoma
College of Medicine - 1986
**Corey L. Detlefs, M.D.**
General Surgery
1130 East McDowell Road, #B-2
Phoenix
University of Arizona
College of Medicine - 1986
**Janice A. Jones, M.D.**
Internal Medicine
350 W. Thomas Road
Phoenix
University of Alabama
School of Medicine - 1989
**Bruce R. Peters, M.D.**
Internal Medicine
1111 E. McDowell Road
Phoenix
Creighton University
School of Medicine - 1989
**Thomas A. Vetto, M.D.**
Emergency Medicine
P.O. Box 5099
Phoenix
University of Oregon
School of Medicine - 1983

## Pima

**Kenneth A. Moss, M.D.**
Obstetrics & Gynecology
Arizona Health Sciences Center
Department of OB/GYN
Tucson
University of California
San Diego School of Medicine - 1981
**Jana Pindur, M.D.**
Pathology
Arizona Health Sciences Center
Pathology, Tucson
Lekarska Fakulta Universita
J. E. Purkyne - 1982
**Patricia L. Wong, M.D.**
Dermatology
Internal Medicine
1550 W. Warren
Department of Dermatology
Tucson
University of California
San Francisco School of
Medicine - 1982

## *Student*

## Maricopa

**Charles T. Crinnian**
7575 N. Dreamy Draw, #209
Phoenix
University of Arizona
College of Medicine - 1990

## Pima

**Seth M. Dubry**
1736 E. 6th Street
Tucson
University of Arizona
College of Medicine - 1993
**Rey R. Palop**
2801 N. Oracle, #410
Tucson
University of Arizona
College of Medicine - 1993
**Kevin Stephens**
2565 E. Water Street
Tucson
University of Arizona
College of Medicine - 1993

# Talk to us!

Have you received special recognition or an award recently from your specialty society or a community organization? Do you know of a colleague who has similarly been honored for medical or community contributions?

If so, please let us know. Call Wendy McCullough at ArMA, 246-8901 in Phoenix or 1-800-482-3480 toll-free statewide. We'd love to share the good news with medical professionals throughout Arizona.

# The AMA Hospital Medical Staff Section Fifteenth Assembly Meeting June 21-25, 1990 Chicago Marriott Hotel Chicago, Illinois

**Highlights of the Annual Meeting will include:**

- an educational program entitled, "Building Effective Hospital Physician Relationships: Ten Success Stories"; Stephen M. Shortell, Ph.D. will present the results of his study on the working relationships between ten selected hospitals and their medical staffs;
- presentation by the AMA-HMSS Governing Council of reports on medical staff issues including the Impact of Hospital Bankruptcy, the Role of Hospital Governing Boards in Professional Review, and Information Sharing Among Medical Staffs;
- recommendation of policy to the House of Delegates on Prioritization of Health Care Expenditures and Notification of Denials by the PRO;
- AMA-HMSS Governing Council elections for the positions of Chairman, Vice-Chairman, Secretary, and one Member-at-large.

**For Information Contact:**

Department of Hospital Medical Staff Services
American Medical Association
535 North Dearborn Street
Chicago, Illinois 60610
Phone (312) 645-4754 or 645-4761

HMSS

# Classified Advertising


**WE BIND YOUR PERIODICALS**

Preserve your medical journals as beautifully bound books. Choose from 30 colors of durable Library Buckram.

**$16.50 Per Volume**
**$20.00 Imitation Leather**
Name imprints (spine) $2.00
Decorative rules $1.00 each
Scattered ad removal $5.00 per volume

Inquire about quantity discounts. **Free** local pickup and delivery on orders of $250 or more. Minimum order is $35.00.

**ROSWELL BOOKBINDING**
**2614 North 29th Avenue**
**Phoenix, Arizona 85009 • (602) 272-9338**

PHYSICIAN OFFICE LABORATORY TESTING is on the rise because it leads to increased medical practice efficiency by providing:

- Better patient care
- Increased patient/physician convenience
- Rapid test results for faster diagnosis and treatment

Let ASSOCIATED LABORATORY CONSULTANTS assist you in:

- Reimbursement maximization (proper CPT usage)
- Optimizing your existing laboratory
- Developing a new laboratory

Call 990-0068 for an appointment to discuss your needs.

Associated Laboratory Consultants, Inc.,
Scottsdale, Arizona

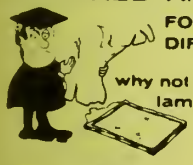
**DANNY T. SEIVERT INSURANCE, INC.**
Professional Programs
for Professional People
70 E. Mitchell Dr., Suite 6
Phoenix, Arizona 85012
263-9090

**CONSUMER AUTO BROKERS**
444 W. Camelback, Ste. 203
Phoenix 85013
274-4400

**A Personalized Car Buying Service**

Al Fann

YOU WORKED HARD



FOR THAT DIPLOMA..
why not have it laminated?

It will last a lifetime....

**THE PLAQUE SHOP**

Wood plaques — Ready to hang
No glass to break — Moisture proof
Dirt proof - - Impressive.
Our plaques are manufactured locally.

ARIZONA LAMINATING SERVICE, INC.
7231 East First Avenue
Scottsdale, Arizona 85251
(602) 945-9338

## *Professional Opportunities*

### Live Among the Redwoods

Successful surgeon seeks partner for busy general and vascular surgery practice on northern California coastline. 85-bed hospital supportive of practice—will provide guarantee and malpractice. Call Gwyneth Anderson for more details about this ideal opportunity at (300) 221-4762, or collect (212) 599-6200. E.G. Todd Associates, 535 Fifth Avenue, Suite 1100, New York, NY 10017.

### Family Practice, Radiology, OB/GYN

Internal Medicine and other specialties needed for small to mid-sized towns in New Mexico and other Sunbelt and Inter-mountain states. Excellent facilities and competitive remuneration packages combine with good schools, outdoor recreation and beautiful locations to provide a quality lifestyle. All inquiries are fully confidential. Call Phyllis or Bruce Moffitt at (505) 898-1114 or send CV to CPS, PO 1163, Corrales, N.M. 87048.

### Board Certified General Surgeon

Wishes to relocate to Arizona. Eight years experience with special interest in diseases of the breast. HMO or hospital based position preferred. Direct inquiries to ArMA, P.O. Box 1990, 810 W. Bethany Home Road, Phoenix, Arizona 85013.

### Phoenix Area

Behavioral Health Program seeking additional adult psychiatrist. Center provides child through adult inpatient, outpatient and partial hospitalization, adult and adolescent CD. Fee-for-services with shared call, or association with existing staff are options. Hospital provides competitive financial support. For more information, call Greg Peterson, E.G. Todd Associates, at (800) 776-7330 or collect (913) 341-7806.

### Locum Tenens Service

Radiologists available for locum tenens or permanent positions. Western Physicians Registry will provide whatever coverage you need for less. Please call Carol Sweig, director, (800) 437-7676.

### Physicians (BC/BE FP or IM)

For unique long-term care program caring for nursing home residents, full or part time. Contact: Medical Director, Long Term Care, Maricopa County, 400 North 7th Street, Phoenix, AZ 85006. (602) 262-8755.

## *Medical Office Space*

### Medical Office Space

1509 sq. ft. built out for doctor in 1987 is now available in Glendale near 53rd Avenue and Northern. Beautiful 1983 Professional Plaza with signage on Northern Avenue. Responsible management. Contact agent: Bill Dutton (602) 241-7916.

### Medical Office

Perfect location—Across from Scottsdale Memorial Hospital-Osborn. Two-office, waiting room and reception. Under $1,000/mo. Call (602) 994-0610.

### Medical Office For Rent

32nd Street near Osborn. 1350 square feet. Ready to move in. $13 per square foot. 3427 N. 32nd St. Call Evelyn. (602)

## *Real Estate*

### Pinetop, Arizona

**$18,000 below appraisal.** Spacious 3-bedroom, 3-bath home on two acres. Year-round stream and pond - solarium - gas and wood heat - sewer - large deck - two-car garage. Across the street from tennis, fishing, equestrian and hiking trails. Absent owner must sell at $122,000. (707) 996-2282.

### Telluride Condo

For sale—3 bedrooms, 2 baths, cathedral ceilings, fully furnished, wood burning stove, walking distance to lift and village. Call (602) 790-6200 — ask for Irma.

## *Miscellaneous*

### Physician Signature Loans

Loans to $50,000. Competitive fixed rates. No collateral. Up to seven years to repay with no pre-payment penalties. Prompt, courteous service. Physicians Service Association, Atlanta, Georgia. (800) 241-6905. Serving MDs for over ten years.

### Retired and Senior Physicians

OMNICARE, a national health care provider is seeking physicians to staff their local clinics. No hassles, remain independent, flexible schedules, and generate extra income. Non invasive, low risk, patient consulting practice. Address all inquiries to John O'Malley, President, 1-800-874-7924.

### Large Loans

Since 1966 specializing in large loans to physicians nationwide from $15,000 to $90,000. Long repayment terms at fixed interest rates. Commitments usually within 48 hours. Woodside Capital Corp., Woodside Capital Building, P.O. Box 368, Woodland Hills, CA 91365. For further information, call (800) 423-5025.

*Classified ads are $20 for the first 50 words and 20 cents for each additional word. Please have your ad to publishing six weeks prior to publication date. Thank you.*

Clinical Medicine

# Physical Diagnosis Versus Modern Technology
## A Review

FAITH T. FITZGERALD, MD, *Sacramento, California*

*The role of physical diagnosis in an age of modern diagnostic technology has been evaluated by investigators assessing specific techniques in a number of areas, though there has been no systematic comprehensive study of the sensitivity, specificity, cost-benefit ratio, and reliability of physical diagnosis relative to technologic diagnostic tools. In a review of published studies comparing physical with nonphysical diagnostic techniques, the startling accuracy of physical diagnosticians in some areas contrasts sharply with the extremely poor correlation of physical findings with autopsy or imaging studies in others. In a time of constricting financial resources, physicians—and those who teach or judge physicians' skills—must begin to compare physical and nonphysical diagnostic techniques rigorously so that the best, safest, and least expensive diagnostic test is chosen in each clinical situation.*

(Fitzgerald FT: Physical diagnosis versus modern technology—A review. West J Med 1990 Apr; 152:377-382)

With their discovery by Wilhelm Conrad Röntgen in 1895, x-rays were incorporated into clinical medicine with astonishing rapidity, and Röntgen was awarded the Nobel prize in 1907.[1(p721)] The physical diagnosis of chest diseases, a meticulously developed craft of observations, sounds, percussion, and maneuvers, seemingly became passé. In the 1980s many chest physicians agreed with the chapter author in a textbook of physical diagnosis that it is best to see a roentgenogram of the chest first and then the patient, as "it can save valuable time to identify in advance the areas that require the most meticulous examination."[2(p226)]

What is the current place of physical diagnosis in an era in which laboratory diagnosis, advanced automatic multichannel serum analyzers, computed tomographic (CT) scans, nuclear medicine, positron emission scanners, magnetic resonance imaging, ultrasonography, and electrodiagnosis offer expanded, often uncanny, entry into the mysteries of the body? Is physical diagnosis in some circumstances arcane, outmoded, an almost cabalistic rite,[3] or does it still have value in the armamentarium of the modern physician?

It appears that there are pragmatic pressures to resuscitate an emphasis on physical diagnosis in the United States. In two surveys of graduates of residency teaching programs, history and physical examination skills were highly rated as important in practice, and the physicians surveyed felt that their training programs had underprepared them in these areas.[4,5] Others have warned of the intrusion of technology into the patient-physician relationship,[6,7] a diminution of time spent with patients at the bedside,[8,9] and the loss of skills in patient-physician negotiation, patient comforting, and psychiatric techniques.[10] Pressures to use the laboratory or nonphysical diagnostic techniques are many: Busy house staff may find it more efficient to write laboratory orders before seeing a patient[11]; new technologies are faddish, and curiosity as well as compulsivity increase their use[12]; the laboratory serves as a "quality control" reference for physicians.[13] Some patients clearly get therapeutic benefit from laboratory tests, expect or demand them, and do not feel well "worked up" without them. Lawyers and third-party payers appear to be impressed by laboratory results, or at least physicians perceive this to be the case.

If physical diagnosis is to be used, it must be assessed in the same rigorous way as are nonphysical diagnostic techniques, but there are difficulties in comparing physical with technologic diagnosis:

- *Unreliability of method.* Whenever a study comparing physical diagnosis with technologic diagnosis is evaluated, it is important to note *who* did the physical diagnosis and *who* interpreted the technologic diagnosis. Studies of the interobserver consistency of physical examination show much variability, but questionable also is the reliability of nonphysical studies.[14] Even when a technologic "gold standard," such as magnetic resonance imaging, is agreed on generally, it may not have been truly well assessed.[15,16]
- *The rapid evolution of technology.* Studies of physical diagnosis versus phonocardiography, or early-generation CT scanners, or the early echo-imaging techniques are of little current value. Of more pertinence, perhaps, is the assessment of the overall accuracy of diagnosis in the face of evolving technologic diagnostic advances. A retrospective analysis of 100 randomly selected autopsies from 1960, 1970, and 1980 showed that in all three decades, despite their vastly different diagnostic tools, 8% to 12% of autopsies revealed major missed diagnoses that, had they been made antemortem, might have prolonged survival. Another 12%

From the Department of Internal Medicine, University of California, Davis, Medical Center, Sacramento, California.

Reprint requests to Faith T. Fitzgerald, MD, Department of Internal Medicine, University of California, Davis, Medical Center, 3120 Primary Care Center, 2221 Stockton Blvd, Sacramento, CA 95817.

of autopsies in these groups showed clinically missed major diagnoses for which therapy would not have changed the outcome. Though the indications for autopsy in each of the three decades might have been very different, the authors of the study thought that an over-reliance on radionuclide scanning, ultrasonography, and CT scanning in several cases contributed directly to the failure to make the major diagnoses.[17]

• *Time, expense, and ease of diagnosis.* In assessing the relative merits of technologic versus physical diagnosis, time and expense become part of the therapeutic ratio. Is physical diagnosis less expensive in dollars than technologic diagnosis? It depends. Clinicians must do physical diagnosis, whereas technicians may do a large part of technologic diagnosis concurrent with clinicians making other use of their time. It may require a skilled neurologist several hours of history taking and physical examination to find a lesion easily demonstrable by CT scan of the brain in half an hour. The time saved may have great value to a busy patient as well as to the clinician. An erroneous diagnosis due to an underuse of the laboratory or to a poor physical examination may be expensive in these litigious times, not to mention disastrous to the patient.

• *Quality control.* Independent assays of serologic studies may allow reproducible (reliable) results. How good is the reliability of physical diagnosticians? Not very, it seems. In studies on the assessment by faculty of physical diagnostic skills of residents and medical students, significant doubts are raised as to our ability as physicians to recognize a good physical examination when we see it.[18-20]

• *Clinical significance of findings.* Even if a technologic assessment is reliable, sensitive, and specific for a given finding, we must ask, "so what?" Much of our clinical advice and prognoses are historically predicated on history and physical examination, or these plus older technologic diagnostic studies. The actual meaning to a patient of a finding uncovered by a newer technology is often uncertain until further experience accumulates. Does a mitral valve prolapse on an echocardiogram mean the same thing as a mitral valve prolapse on auscultation?[21] Has the use of ultrasonography in the diagnosis of appendicitis[22] improved or worsened[23] patient outcome in this disease? Too sensitive a diagnostic technology, even if highly specific, could conceivably even create disease when the condition detected has a lesser morbidity than its diagnosis and therapy. Transrectal ultrasonography, for example, has been reported to have a detection rate for prostatic carcinoma two times greater than that with digital examination.[24] How many men who would normally have died with, but were not symptomatically bothered by, a prostatic cancer would be frightened by its detection and injured by its biopsy or removal? The risk-benefit ratio for this and other highly sensitive diagnostic tests remains to be determined.

Physicians still believe that the history and physical examination have value in diagnosis, with the history overwhelmingly the most useful diagnostic tool.[25,26] The value of the physical examination has been studied and compared with that of technologic diagnosis in many areas of the body, though not extensively nor systematically. A brief literature review, arranged along the lines of a standard physical examination, illustrates not only what has been done to date, but also the need for more—and more stringent—comparative studies.

## General Examinations

Most experienced clinicians value an as-yet-unquantified ability to distinguish a sick from a not-so-sick patient, as well as the experientially derived skill of defining or, at the least, identifying a classic syndromic general appearance. To what degree these assessments are valid remains unstudied in any formal sense.

Physical examiners judging patients' nutritional status agreed in 81% of cases, and their opinion correlated well with laboratory evidence. Clinical morbidity—number of days in hospital, incidence of infection, need for antibiotics—related well to clinical assessment.[27] In a prospective evaluation of 50 patients, there was a significant correlation between a measured hemoglobin concentration and the color tint of the lower lid conjunctivae, nail bed rubor and blanching, and the rubor of the palmar crease. It appears that both the presence and the degree of anemia can be reliably estimated clinically by a careful physical examination.[28] In patients admitted to a medical intensive care unit, clinical examination was found inadequate to predict right-sided heart catheter findings in critically ill patients without myocardial infarction. In nearly half the patients in this study, the data obtained by right-sided heart catheterization resulted in important changes in therapy.[29] In a similar study, Unger and associates looked at 14 patients with the adult respiratory distress syndrome and found no clinical criteria that would allow an examiner to accurately distinguish those with left ventricular failure from those without it.[30] A physical examination may be of less value in the diagnosis in a critically ill patient. There are difficulties inherent in the physical examination of patients in an intensive care unit, including the physical impediments of tubes, lines, and monitors; potentially high levels of ambient noise may impair auscultation (in nonintensive care patient rooms, peak noise levels of 70 decibels have been recorded, equal to the noise generated by a vacuum cleaner).[31] Nonetheless, the high frequency of incorrect clinical predictions in seriously ill patients merits caution.

## Vital Signs

Though the blood pressure is perhaps the most frequently measured of all physical findings, numerous studies have shown that the reliability of blood pressure measurements is poor. A sphygmomanometric measurement of the systolic blood pressure using auscultation underestimates the direct systolic pressure by an average of 16 to 17 mm of mercury[32] and varies by the age of the patient,[33] cuff size,[34] and arterial compliance.[35] The auscultatory blood pressure also varies depending on arm position,[36,37] pressure of the head of the stethoscope on the artery,[38] and even the profession of the person taking the blood pressure.[39] How these variations relate to the long-term clinical prognosis of a "hypertensive" patient remains unknown, as does the question of whether intra-arterial or sphygmomanometric blood pressure is the better predictor of clinical sequelae.

Fever, an ancient sign of disease, has been studied. Eisenberg and colleagues found that emergency department physicians admitted to the hospital febrile patients with subsequently positive blood cultures far more often than they admitted febrile patients who turned out to have negative blood cultures, suggesting that clinical judgment could predict bacteremia in a patient.[40] A subsequent study, however, has found that emergency department physicians' diagnostic

predictions did not correlate with a final diagnosis of infective endocarditis in febrile intravenous drug abusers.[41] Similarly, Makadon and co-workers found house-staff predictions of bacteremia in febrile inpatients to be inaccurate, concluding that clinical judgment is not an adequate substitute for blood cultures in this population.[42]

### Eye

Because intraocular pressure measurements do not correlate directly with clinically significant glaucoma, it is accepted that ophthalmoscopy by a skilled examiner gives fewer falsely abnormal results than tonometry in detecting glaucoma.[43]

### Head, Ears, Nose, and Throat

In the evaluation of sphenoid sinusitis, physical examination is useful in providing clues (turbinate pus, fever, neurologic changes) but not diagnostic: CT scan is held to be the diagnostic test of choice.[44] The opacity of the maxillary sinuses when illuminated by a Welch-Allyn-Finnoff transilluminator was a sensitive and specific predictor of abnormal sinus aspirates.[45] Physical examination of the pharynx in pharyngitis does not distinguish viral from bacterial infection.[46]

### Breast

An early study suggested that the most rewarding method of screening for breast cancer was the annual clinical examination by a physician[47]: 1,000 women were observed prospectively, comparing the annual clinical examination, mammography, thermography, and breast self-examination. Of 23 malignant solid lesions first detected clinically in this study, only 4 showed changes on mammography. Other investigators, however, have maintained the superiority of mammography to clinical examination, with the best sensitivity of detection obtained by combining the use of both.[48,49]

### Chest

Spiteri and colleagues studied physician reliability in eliciting physical signs in the examination of the chest and found that there was generally poor agreement among physicians about particular chest signs. More than 25% of physicians' diagnoses were incorrect. Agreement among the physicians was greatest for percussion note, wheezing, and the presence of pleural rubs. It was little better than chance for tactile fremitus, pectoriloquy, and displacement of the trachea.[50]

In a study designed to assess the skill of private internists in recognizing obstructive lung disease by physical findings alone compared with pulmonary function tests, there was immense variation among the physicians in signs detected and poor ability to predict the presence or absence of abnormal physiologic measurements of respiratory function. Decreased breath sounds were the most reliable single sign detected, with barrel chest, decreased chest expansion, impaired cardiac dullness, the use of accessory muscles of respiration, an absence of the cardiac point of maximal impulse, cyanosis, and decreased diaphragmatic excursion following in order. Impaired liver dullness and decreased diaphragmatic movement showed no statistically important relation to emphysema by pulmonary function tests.[51]

Perhaps the absence of a value of the physical detection of diaphragmatic excursion in evaluating emphysema is illuminated by the study of Williams and associates in which diaphragmatic percussion showed wide interobserver variation and poor correlation with diaphragmatic excursion as measured by inspiratory-expiratory chest roentgenograms.[52]

Physical examination to detect or quantify obstructive lung disease may be unreliable compared with pulmonary function studies and chest roentgenography, but does this make a difference in management? Owens and co-workers assessed by history and physical examination 100 patients with lung disease in an outpatient clinic, classifying them clinically as improved, stable, or worse. None of those who were clinically improved and but 3% of the stable patients had any change in clinical management as a consequence of spirometry or chest x-ray film; 29% of those clinically categorized as deteriorated had their management plans modified after a review of their spirograms and chest films.[53]

Only 32% of fatal pulmonary emboli in patients admitted to hospital are clinically suspected during life,[54] and the history and physical examination show low sensitivity and specificity for diagnosis compared with pulmonary angiography, with its sensitivity of 98% and specificity of greater than 99%.[55]

Numerous attempts have been made to find good clinical predictors of the severity of asthma, the need for admitting to a hospital, and the likelihood of relapse, using both physical and spirometric examinations,[56] with arguable success.[56-58] The severity of acute episodes of asthma is imperfectly reflected by the signs and symptoms of the disease, though sternocleidomastoid retraction,[59] a disturbance of consciousness, unequivocal central cyanosis, pulsus paradoxus,[60,61] sitting upright, and diaphoresis[61] have all been shown to reflect severe disease. The forced expiratory volume in 1 second has been said to be a more reliable guide to adequate therapy for discharge from an emergency department in a patient with acute asthma than the disappearance of dyspnea, the diminution of labored breathing, a reduction of wheezing, or loss of a pulsus paradoxus or sternocleidomastoid retraction.[62] Patients have been shown to be capable of greater accuracy in assessing their own peak expiratory flow rates than are the physicians examining them.[63]

### Cardiovascular

There has been a recent reawakening to the possibilities of the precise cardiac diagnosis of heart murmurs by a variety of bedside maneuvers,[64-70] but only some investigators address the question of a physician's skill, investment of clinician's time, and limitations in sensitivity and specificity of each maneuver—Valsalva's, Müller's, isometric handgrip, and so forth.[7] Apparently a combination of these skills and maneuvers applied by an experienced clinician may be extraordinarily revealing.[64] Modern cardiac diagnostic technology can be retrospectively compared with expert clinical diagnosticians. Two decades ago, before the widespread use of technologic diagnosis in cardiac disease, Pestana and colleagues found that in patients with congenital heart disease, 80% of clinical diagnoses were confirmed as "completely accurate" at operation.[72] In the remaining 20%, the clinical diagnosis was actually confirmed, but an unsuspected additional lesion was also present: the additional lesion, however, made a major difference in only 3.7% of the total group. A more recent survey of the usefulness of M-mode echocardiography, chest roentgenography, and electrocardiography in discriminating between the presence or absence of heart disease in children with heart murmurs concluded that the tests

were unlikely to add anything to a qualified pediatric cardiologist's accurate assessment of "definite heart disease" or "no heart disease."[73]

Echocardiography adds significantly to a clinician's ability to diagnose and quantitate aortic stenosis,[74] and auscultation of aortic insufficiency is less sensitive and specific than Doppler echocardiography (though auscultation is more sensitive than M-mode or two-dimensional echocardiography in the diagnosis of aortic insufficiency).[75] Echocardiography is clearly more sensitive than clinical examination for detecting pericardial effusions.[76] The urgent need for further studies to establish the practical utility of auscultation versus echocardiography is emphasized by the exquisite sensitivity of echocardiography in detecting valvular regurgitation: does tricuspid, mitral, or even pulmonic insufficiency[77] by echocardiogram have the same meaning as that detected by physical examination? It appears not.

It is generally acknowledged that electrocardiograms in an emergency department should seldom if ever alter the ultimate decision, based on the history and physical examination, of whether or not to admit a patient with chest pain.[78] Vascular disease elsewhere, congestive heart failure, hypertension, ventricular gallops, and cardiomegaly are surprisingly poor predictors of significant coronary artery disease, though a history of risk factors, previous myocardial infarction, and an abnormal electrocardiogram are useful predictors.[79] A physical examination is reliable in excluding hemodynamically significant right ventricular infarction in a patient with an inferior wall myocardial infarction who has neither elevated jugular venous pressure nor Kussmaul's sign.[80]

In patients with a clear clinical diagnosis of infective endocarditis, M-mode echocardiography showed vegetations in but 49%, with two-dimensional echocardiogram revealing vegetations in 80%.[81]

The bedside determination of the duration and size of the cardiac apical impulse predicted left ventricular hypertrophy by angiography more accurately than did electrocardiography or chest roentgenography,[82] but the location of the left ventricular impulse was less reliable.[82,83]

When cardiologists were asked to estimate the left ventricular ejection fraction compared with gated blood pool scan measurements, 56% of physicians' estimates were accurate, 17% underestimated, and 27% overestimated.[84] In a similar study, the clinical cardiologist was able to predict in 61% of cases whether or not the left ventricular ejection fraction would be normal, mildly to moderately reduced, or severely reduced in 99 patients with known coronary artery disease studied by radionuclide ventriculography.[85] Cease and Nicklas have proposed a formula using direct heart rate, blood pressure, and heart size on chest film that can predict a radionuclide ventriculographic ejection fraction of less than 40% with 87% sensitivity and 83% specificity.[86]

In 458 diabetic patients, noninvasive testing was found to reveal peripheral arterial disease in nearly a third of patients without a history of claudication and 20% of those with normal findings on clinical examination.[87]

## Abdomen

Abdominal aortic aneurysm is ill diagnosed by physical examination compared with arteriography[88] and ultrasonography,[89] although in the latter study clinicians could accurately detect all aortic aneurysms in the study patients with abdominal girths less than 100 cm. Overall, however, the positive predictive value of a definite or suggestive pulsatile abdominal mass was but 35%.[89]

Abdominal bruits were found in almost 16% of normal persons in one study and in 64% of those with renal artery stenosis, though one could not predict accurately from the side of the ausculted bruit the location of the vascular stenosis.[90] A more recent study has confirmed the insensitivity of abdominal bruits in predicting renal arterial stenoses or occlusions found by angiography.[91] In patients younger than 25 years, the frequency of abdominal bruits or murmurs may be as high as 44%.[92] In patients with known renovascular hypertension, the presence of a systolic-diastolic abdominal bruit was more sensitive than upright plasma renin activity but far less sensitive than rapid-sequence urography in defining their disease.[93]

A palpable spleen has been detected in 2.86% of 2,200 routinely examined college students.[94] A palpable spleen strongly suggests enlargement of that organ and is more sensitive than increased splenic size by abdominal roentgenography, but nonpalpable spleens may be enlarged.[95] Of 92 cases of splenomegaly by nuclear scan, only 26 (28%) were determined by physical examination.[96] Splenic percussion may be a more sensitive sign by physical examination than palpation and compared well with splenic size by nuclear scan.[97]

A good correlation is found between the liver size on nuclear scan and the estimated liver span by percussion in the right midclavicular and midsternal line, but little relationship exists between the liver size by scan and a clinical estimate of the position of the liver border.[98] A palpable liver appears to be a poor index of hepatomegaly, though one may somewhat more accurately rule out hepatomegaly if the liver is not palpable.[95,96]

In men admitted to a hospital with liver disease, physical examination was compared with ultrasonography of the abdomen in the detection of ascites. The positive predictive value of shifting dullness and prominent fluid waves was low—51% and 73%, respectively. In those patients with an increased prothrombin time, however, the presence of a prominent fluid wave had a 96% predictive value for ascites. In contrast, in those with a normal prothrombin time, both shifting dullness and prominent fluid waves were usually falsely abnormal findings.[99]

## Musculoskeletal

Most authors agree that the history and physical examination are the most specific and sensitive studies available for the diagnosis of low back pain[100–102] and that in the absence of fever, a history suggestive of malignancy, major trauma, neurologic defects, corticosteroid, illicit drug or alcohol use, or advanced age, further studies are often legally rather than medically inspired.[102] The selection of patients with injured extremities who need x-ray films has been similarly argued to be well guided by history and physical examination alone.[103]

## Neurologic

In a study of 25 patients with cerebral infarction unassociated with extracranial cerebrovascular disease, cerebral angiography was diagnostic in only a third of cases and altered the preangiographic diagnosis in only one case by revealing a previously unsuspected embolus.[104] A study on the

usefulness of CT scans in patients with a clinically diagnosed first stroke suggested that it was useful in a minority (up to 28%) who can be selected on simple clinical criteria.[105] Advanced techniques of echocardiography have been useful in detecting clinically silent atrial septal defects with paradoxic cerebral embolism.[106,107]

The history and physical examination appear to be the best diagnostic tools available for evaluating syncope,[108,109] sufficient in 85% of patients in whom a diagnosis could be established.[110]

Routine skull x-ray films and CT scans after head trauma were not found to be worthwhile unless specific criteria, established by history and physical examination, were present.[111,112] Similarly, patients with headache and a normal neurologic examination were found not to benefit by CT scan of the brain.[113] In patients with alcohol withdrawal seizures, a neurologic examination predicts which patients need prompt CT scanning of the brain, and the absence of focal defects or signs of acute head trauma suggests that a CT scan will be unhelpful.[114] In demented patients, studies suggest that the history and physical examination are superior to CT scan of the brain and other studies in determining the cause of their dementia.[115,116] The prognosis in patients with nontraumatic coma is similarly best determined by a careful evaluation of the neurologic system over the first few days of hospital admission.[117] In 209 patients studied with intentional drug overdose, a toxicologic analysis from the laboratory agreed with the clinical impression in 47% of cases, and though clinically unsuspected drugs were found in 27% of cases, this led to a change in therapy in only three patients and in none had a major influence on the outcome.[118]

## Conclusion

It is clear that the best interest of patients lies in a judicious combination of a careful history and physical examination and directed laboratory studies. The physical examination has some clear advantages over laboratory studies, in that it allows therapeutic touching and a warmer interaction between patient and physician, renders the physician more autonomous in his or her diagnostic skills, and may be at least as accurate as many more expensive and time-consuming laboratory diagnostic studies. At the same time, certain time-honored physical examination techniques are being questioned as to their validity and relative merits compared with the rapidly evolving wonders of technologic diagnostic techniques.

Modern physicians, under the pressures of curiosity, compulsivity, insecurity, and the imagined or real threat of unpleasant legal or economic consequences, seem more comfortable with technologic than with physical diagnosis. Because of constricting resources and increasing alienation of patients from their physicians, it is imperative to scrupulously reexamine the role of the physical examination in modern diagnosis. Only in this way will we be able to preserve and expand the best of physical diagnosis and discard the remainder as historical remnants of an earlier, albeit simpler, time.

### REFERENCES


1. Garrison FH: An Introduction to the History of Medicine, 4th Ed. Philadelphia, WB Saunders, 1929
2. Judge RD, Zuidema GD, Fitzgerald FT (Eds): Clinical Diagnosis—A Physiologic Approach, 4th Ed. Boston, Little, Brown, 1989
3. Lacombe M: A piece of my mind—The cabalist. JAMA 1988; 259:3045
4. Kern DC, Parrino TA, Korst DR: The lasting value of clinical skills. JAMA 1985; 254:70-76
5. Mandel JH, Rich EC, Luxenberg MG, et al: Preparation for practice in internal medicine—A study of ten years of residency graduates. Arch Intern Med 1988; 148:853-856
6. Rabkin MT: Medical education—Three-legged stool or five-wheeled work chair? West J Med 1988; 149:103-107
7. Bosk CL: Occupational rituals in patient management. N Engl J Med 1980; 303:71-76
8. Blanchard CG, Ruckdeschel JC, Blanchard EB, et al: Interactions between oncologists and patients during rounds. Ann Intern Med 1983; 99:694-699
9. Shankel SW, Mazzaferri EL: Teaching the resident in internal medicine—Present practices and suggestions for the future. JAMA 1986; 256:725-729
10. McCue JD: Training internists: Insights from private practice. Am J Med 1981; 71:475-479
11. Baldwin JG Jr: Being a better house officer. Am J Med 1985; 78:369-370
12. Showstack JA, Schroeder SA, Matsumoto MF: Changes in the use of medical technologies, 1972-1977: A study of 10 inpatient diagnoses. N Engl J Med 1982; 306:706-712
13. Handler RP: Diagnostic tests necessary to maintain clinical skills (Letter). N Engl J Med 1979; 300:507
14. Koran LM: The reliability of clinical methods, data and judgments. N Engl J Med 1975; 293:642-646, 695-701
15. Cooper LS, Chalmers TC, McCally M, et al: The poor quality of early evaluations of magnetic resonance imaging. JAMA 1988; 259:3277-3280
16. Sheps SB: Technological imperatives and paradoxes (Editorial). JAMA 1988; 259:3312-3313
17. Goldman L, Sayson R, Robbins S, et al: The value of the autopsy in three medical eras. N Engl J Med 1983; 308:1000-1005
18. Wolliscroft JO, Stross JK, Silva J Jr: Clinical competence certification: A critical appraisal. J Med Educ 1984; 59:799-805
19. Elliot DL, Hickam DH: Evaluation of physical examination skills—Reliability of faculty observers and patient instructors. JAMA 1987; 258:3405-3408
20. Stillman PL, Swanson DB, Smee S, et al: Assessing clinical skills of residents with standardized patients. Ann Intern Med 1986; 105:762-771
21. Krivokapich J, Child JS, Dadourian BJ, et al: Reassessment of echocardiographic criteria for diagnosis of mitral valve prolapse. Am J Cardiol 1988; 61:131-135
22. Puylaert JB, Rutgers PH, Lalisang RI, et al: A prospective study of ultrasonography in the diagnosis of appendicitis. N Engl J Med 1987; 317:666-669
23. Schwartz SI: Tempering the technological diagnosis of appendicitis (Editorial). N Engl J Med 1987; 317:703-704
24. Lee F, Littrup PJ, Torp-Pedersen ST, et al: Prostate cancer: Comparison of transrectal US and digital rectal examination for screening. Radiology 1988; 168:389-394
25. Hampton JR, Harrison MJ, Mitchell JR, et al: Relative contributions of history-taking, physical examination and laboratory investigation to diagnosis and management of medical outpatients. Br Med J 1975; 2:486-489
26. Rich EC, Crowson TW, Harris IB: The diagnostic value of the medical history—Perceptions of internal medicine physicians. Arch Intern Med 1987; 47:1957-1960
27. Baker JP, Detsky AS, Wesson DE, et al: Nutritional assessment—A comparison of clinical judgment and objective measurements. N Engl J Med 1982; 306:969-972
28. Strobach RS, Anderson SK, Doll DC, et al: The value of the physical examination in the diagnosis of anemia—Correlation of the physical findings and the hemoglobin concentration. Arch Intern Med 1988; 148:831-832
29. Connors AF, McCaffree DR, Gray BA: Evaluation of right heart catheterization in the critically ill patient without acute myocardial infarction. N Engl J Med 1983; 308:263-267
30. Unger IKM, Shibel EM, Moser KM: Detection of left ventricular failure in patients with adult respiratory distress syndrome. Chest 1975; 67:8-13
31. Topf M: Noise pollution in the hospital. N Engl J Med 1983; 309:53-54
32. Finnie KJC, Watts DG, Armstrong PW: Biases in the measurement of arterial pressure. Crit Care Med 1984; 12:965-968
33. Hla KM, Feussner JR: Screening for pseudohypertension—A quantitative, noninvasive approach. Arch Intern Med 1988; 148:673-676
34. Burch GE, Shewey L: Sphygmomanometric cuff size and blood pressure recordings. JAMA 1973; 225:1215-1218
35. Messerli FH, Ventura HO, Amodeo C: Osler's maneuver and pseudohypertension. N Engl J Med 1985; 312:1548-1551
36. Kroenke K: Sphygmomanometry: The correct arm position (Letter). West J Med 1984; 140:459-460
37. Silverberg DS, Shemesh E, Iaina A: The unsupported arm: A cause of falsely raised blood pressure readings. Br Med J 1977; 2:1331
38. Londe S, Klitzner TS: Auscultatory blood pressure measurement—Effect of pressure on the head of the stethoscope. West J Med 1984; 141:193-195
39. Pickering TG, James GD, Boddie C, et al: How common is white coat hypertension? JAMA 1988; 259:225-228
40. Eisenberg JM, Rose JD, Weinstein AJ: Routine blood cultures from febrile outpatients—Use in detecting bacteremia. JAMA 1976; 236:2863-2865
41. Marantz PR, Linzer M, Feiner CL, et al: Inability to predict diagnosis in febrile intravenous drug abusers. Ann Intern Med 1987; 106:823-828
42. Makadon HJ, Bor D, Friedland G, et al: Febrile inpatients—Houseofficers' use of blood cultures. J Gen Intern Med 1987; 2:293-297
43. Schwartz B: Current concepts in ophthalmology—The glaucomas. N Engl J Med 1978; 299:182-184

44. Lew D, Southwick FS, Montgomery WW, et al: Sphenoid sinusitis—A review of 30 cases. N Engl J Med 1983; 309:1149-1154

45. Evans FO Jr, Sydnor JB, Moore WE, et al: Sinusitis of the maxillary antrum. N Engl J Med 1975; 293:735-739

46. Valkenburg HA: Streptococcal pharyngitis and tonsillitis, *In* Braude AI, Davis CE, Fierer J (Eds): Infectious Diseases and Medical Microbiology, 2nd Ed. Philadelphia, WB Saunders, 1986, pp 715-718

47. Mahoney LJ, Bird BL, Cooke GM: Annual clinical examination: The best available screening test for breast cancer. N Engl J Med 1979; 301:315-316

48. O'Malley MS, Fletcher SW: US Preventive Services Task Force—Screening for breast cancer with breast self-examination. JAMA 1987; 256:2196-2203

49. Hicks MJ, Davis JR, Layton JM, et al: Sensitivity of mammography and physical examination of the breast for detecting breast cancer. JAMA 1979; 242:2080-2083

50. Spiteri MA, Cook DG, Clarke SW: Reliability of eliciting physical signs in examination of the chest. Lancet 1988; 1:873-875

51. Schneider IC, Anderson AE Jr: Correlation of clinical signs with ventilatory function in obstructive lung disease. Ann Intern Med 1965; 62:477-485

52. Williams TJ, Ahmad D, Morgan WK: A clinical and roentgenographic correlation of diaphragmatic movement. Arch Intern Med 1981; 141:878-880

53. Owens MW, Kinasewitz GT, Lambert RS, et al: Influence of spirometry and chest roentgenography on the management of pulmonary outpatients. Arch Intern Med 1987; 147:1966-1969

54. Rubinstein I, Murray D, Hoffstein V: Fatal pulmonary emboli in hospitalized patients—An autopsy study. Arch Intern Med 1988; 148:1425-1426

55. Lo B: The diagnosis of pulmonary embolus. West J Med 1982; 136:542-545

56. Fischl MA, Pitchenik A, Gardner LB: An index predicting relapse and need for hospitalization in patients with acute bronchial asthma. N Engl J Med 1981; 305:783-789

57. Rose CC, Murphy JG, Schwartz JS: Performance of an index predicting the response of patients with acute bronchial asthma to intensive emergency department treatment. N Engl J Med 1984; 310:573-577

58. Centor RM, Yarbrough B, Wood JP: Inability to predict relapse in acute asthma. N Engl J Med 1984; 310:577-580

59. McFadden ER Jr, Kiser R, deGroot WJ: Acute bronchial asthma—Relations between clinical and physiologic manifestations. N Engl J Med 1973; 288:221-225

60. Rebuck AS, Read J: Assessment and management of severe asthma. Am J Med 1971; 51:788-798

61. Brenner BE, Abraham E, Simon RR: Position and diaphoresis in acute asthma. Am J Med 1983; 74:1005-1009

62. Kelsen SG, Kelsen DP, Fleegler BF, et al: Emergency room assessment and treatment of patients with acute asthma—Adequacy of the conventional approach. Am J Med 1978; 64:622-628

63. Shim CS, Williams MH Jr: Evaluation of the severity of asthma: Patients versus physicians. Am J Med 1980; 68:11-13

64. Lembo NJ, Dell'Italia LJ, Crawford MH, et al: Bedside diagnosis of systolic murmurs. N Engl J Med 1988; 318:1572-1578

65. Craige E: Should auscultation be rehabilitated? N Engl J Med 1988; 318:1611-1613

66. Lembo NJ, Dell'Italia LJ, Crawford MH, et al: Diagnosis of left-sided regurgitant murmurs by transient arterial occlusion: A new maneuver using blood pressure cuffs. Ann Intern Med 1986; 105:368-370

67. Kramer DS, French WJ, Criley JM: The postextrasystolic murmur response to gradient in hypertrophic cardiomyopathy. Ann Intern Med 1986; 104:772-776

68. Smith ND, Raizada V, Abrams J: Auscultation of the normally functioning prosthetic valve. Ann Intern Med 1981; 95:594-598

69. Cochran PT: Bedside aids to auscultation of the heart. JAMA 1978; 239:54-55

70. Maisel AS, Atwood JE, Goldberger AL: Hepatojugular reflux: Useful in the bedside diagnosis of tricuspid regurgitation. Ann Intern Med 1984; 101:781-782

71. Rothman A, Goldberger AL: Aids to cardiac auscultation. Ann Intern Med 1983; 99:346-353

72. Pestana C, Weidman WH, Swan HJC, et al: Accuracy of preoperative diagnosis in congenital heart disease. Am Heart J 1966; 72:446-450

73. Newberger JW, Rosenthal A, Williams RG, et al: Noninvasive tests in the initial evaluation of heart murmurs in children. N Engl J Med 1983; 308:61-64

74. Hoagland PM, Cook EF, Wynne J, et al: Value of noninvasive testing in adults with suspected aortic stenosis. Am J Med 1986; 80:1041-1050

75. Grayburn PA, Smith MD, Handshoe R, et al: Detection of aortic insufficiency by standard echocardiography, pulsed Doppler echocardiography and auscultation—A comparison of accuracies. Ann Intern Med 1986; 104:599-605

76. Riba AL, Morganroth J: Unsuspected substantial pericardial effusions detected by echocardiography. JAMA 1976; 236:2623-2625

77. Pieres JE, Smith CA, Meltzer VN: Pulmonic valve insufficiency: A common cause of transient diastolic murmurs in renal failure. Ann Intern Med 1985; 104:497-502

78. Hoffman JR, Igarashi E: Influence of electrocardiographic findings on admission decisions in patients with acute chest pain. Am J Med 1985; 79:699-707

79. Pryor DB, Harrell FE Jr, Lee KL, et al: Estimating the likelihood of significant coronary artery disease. Am J Med 1983; 75:771-780

80. Dell'Italia LJ, Starling MR, O'Rourke RA: Physical examination for exclusion of hemodynamically important right ventricular infarction. Ann Intern Med 1984; 99:608-611

81. Melvin ET, Berger M, Lutzker LG, et al: Noninvasive methods for detection of valve vegetations in infective endocarditis. Am J Cardiol 1981; 47:271-278

82. Conn RD, Cole JS: The cardiac apex impulse—Clinical and angiographic correlations. Ann Intern Med 1971; 75:186-191

83. Eilen SD, Crawford MH, O'Rourke RA: Accuracy of precordial palpation for detecting increased left ventricular volume. Ann Intern Med 1983; 99:628-630

84. Eagle KA, Quertermous T, Singer DE, et al: Left ventricular ejection fraction—Physician estimates compared with gated blood pool scan measurements. Arch Intern Med 1988; 148:882-885

85. Mattleman SJ, Hakki AH, Iskansrian AS, et al: Reliability of bedside evaluation in determining left ventricular function: Correlation with left ventricular ejection fraction determined by radionuclide ventriculography. J Am Coll Cardiol 1983; 1:417-420

86. Cease KB, Nicklas JM: Prediction of left ventricular ejection fraction using simple quantitative clinical information. Am J Med 1986; 81:429-436

87. Marinelli MR, Beach KW, Glass MJ, et al: Noninvasive testing vs clinical evaluation of arterial disease—A prospective study. JAMA 1979; 241:2031-2034

88. Brewster DC, Retana A, Waltman AC, et al: Angiography in the management of aneurysms of the abdominal aorta. N Engl J Med 1975; 292:822-825

89. Lederle FA, Walker JM, Reinke DB: Selective screening for abdominal aortic aneurysms with physical examination and ultrasound. Arch Intern Med 1988; 148:1753-1756

90. Julius S, Stewart BH: Diagnostic significance of abdominal murmurs. N Engl J Med 1967; 276:1175-1178

91. McLoughlin MJ, Colapinto RF, Hobbs BB: Abdominal bruits—Clinical and angiographic correlation. JAMA 1975; 232:1238-1242

92. Rivin AH: Abdominal vascular sounds. JAMA 1972; 221:688-690

93. Grim CE, Luft FC, Weinberger MH, et al: Sensitivity and specificity of screening tests for renal vascular hypertension. Ann Intern Med 1979; 91:617-622

94. McIntyre OR, Ebaugh FG Jr: Palpable spleens in college freshmen. Ann Intern Med 1967; 66:301-306

95. Riemenschneider PA, Whalen JP: The relative accuracy of estimation of enlargement of the liver and spleen by radiologic and clinical methods. AJR 1965; 94:462-468

96. Halpern S, Coel M, Ashburn W, et al: Correlation of liver and spleen size—Determinations by nuclear medicine studies and physical examination. Arch Intern Med 1974; 134:123-124

97. Castell DO: The spleen percussion sign—A useful diagnostic technique. Ann Intern Med 1967; 67:1265-1267

98. Castell DO, O'Brien KD, Muench H, et al: Estimation of liver size by percussion in normal individuals. Ann Intern Med 1969; 70:1183-1189

99. Cummings S, Papadakis M, Melnick J, et al: The predictive value of physical examinations for ascites. West J Med 1985; 142:633-636

100. Calin A: HLA-B27: To type or not to type. Ann Intern Med 1980; 92(pt 1):208-211

101. Frymoyer JW: Back pain and sciatica. N Engl J Med 1988; 318:291-300

102. Deyo RA: Early diagnostic evaluation of low back pain (Clinical Review). J Gen Intern Med 1986; 1:328-338

103. Brand DA, Frazier WH, Kohlhepp WC, et al: A protocol for selecting patients with injured extremities who need x-rays. N Engl J Med 1982; 306:333-339

104. Stillman MJ, Ronthal M, Kleefield J, et al: Cerebral infarction: Shortcomings of angiography in the evaluation of intracranial cerebrovascular disease in 25 cases. Medicine (Baltimore) 1987; 66:298-308

105. Sandercock P, Molyneux A, Warlow C: Value of computed tomography in patients with stroke: Oxfordshire Community Stroke Project. Br Med J (Clin Res) 1985; 290:193-197

106. Harvey JR, Teague SM, Anderson JL, et al: Clinically silent atrial septal defects with evidence for cerebral embolization. Ann Intern Med 1986; 105:695-697

107. Lechat PH, Mas JL, Lascault G, et al: Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 1988; 318:1148-1152

108. Kapoor WN, Karpf M, Wieand S, et al: A prospective evaluation and follow-up of patients with syncope. N Engl J Med 1983; 309:197-204

109. Gulamhusein S, Naccarelli GV, Ko PT, et al: Value and limitations of clinical electrophysiologic study in assessment of patients with unexplained syncope. Am J Med 1982; 73:700-705

110. Day SC, Cook EF, Funkenstein H: Evaluation and outcome of emergency room patients with transient loss of consciousness. Am J Med 1982; 73:15-23

111. Cummins RO, LoGerfo JP, Inui TS, et al: High-yield referral criteria for posttraumatic skull roentgenography—Response of physicians and accuracy of criteria. JAMA 1980; 244:673-676

112. Masters SJ, McClean PM, Arcarese JS, et al: Skull x-ray examinations after head trauma—Recommendations by a multidisciplinary panel and validation study. N Engl J Med 1987; 316:84-91

113. Larson EB, Omenn GS, Lewis H: Diagnostic evaluation of headache—Impact of computerized tomography and cost-effectiveness. JAMA 1980; 243:359-362

114. Feussner JR, Linfors EW, Blessing CL, et al: Computed tomography brain scanning in alcohol withdrawal seizures—Value of the neurologic examination. Ann Intern Med 1981; 94:519-522

115. Larson EB, Mack LA, Watts B, et al: Computed tomography in patients with psychiatric illnesses—Advantage of a 'rule-in' approach. Ann Intern Med 1981; 95:360-364

116. Consensus Conference, Office of Medical Applications of Research, National Institutes of Health, Bethesda, Md: Differential diagnosis of dementing diseases. JAMA 1987; 258:3411-3416

117. Levy DE, Bates D, Caronna JJ, et al: Prognosis in nontraumatic coma. Ann Intern Med 1981; 94:293-301

118. Brett AS: Implications of discordance between clinical impression and toxicology analysis in drug overdose. Arch Intern Med 1988; 148:437-441

# Current Management of the Wolff-Parkinson-White Syndrome

ANDREW ARAI, MD, *and* JACK KRON, MD, *Portland*

*The Wolff-Parkinson-White syndrome is a multifaceted disorder that ranges from asymptomatic to life threatening. Accounting for approximately 20% of cases of paroxysmal supraventricular tachycardia and with a prevalence perhaps as high as 1 per 500, it is far from a rare disorder. Considering the potentially lethal complications following the administration of digoxin or verapamil, all physicians treating arrhythmias should know when to suspect the Wolff-Parkinson-White syndrome. A careful review of electrocardiograms helps identify cases of the disorder despite a wide range of findings that may mimic other conditions. Major advances in the efficacy of surgical procedures to cure this syndrome make this a reasonable alternative to life-long medical therapy for many patients. Unfortunately, available diagnostic tests lack the positive predictive value to reliably distinguish patients at risk of sudden death. This review is an update for general internists of the major developments in the evaluation and treatment of the disorder and provides specific examples helpful in differentiating these patients.*

(Arai A, Kron J: Current management of the Wolff-Parkinson-White syndrome. West J Med 1990 Apr; 152:383-391)

Since the initial case report in 1915[1] and the formal characterization of the Wolff-Parkinson-White syndrome in 1930,[2] an extensive body of literature concerning the significance and treatment of the disorder has been published. In 1933 Wolferth and Wood postulated an accessory pathway to explain the electrocardiographic findings of the syndrome,[3] but an accessory pathway in a patient with this disorder was not histologically confirmed until 1943.[4] Although initially considered a benign syndrome, cases of sudden death associated with it were reported as early as 1934.[5] A mechanism attributing ventricular fibrillation to the presence of the accessory pathway during atrial fibrillation was described in 1971.[6] Durrer and Roos introduced epicardial mapping to advance the physiologic understanding of preexcitation in 1967.[7] Subsequently the technique of programmed electrical stimulation of the heart evolved to become a commonly available clinical tool to evaluate patients with the syndrome.

With a macroscopic anatomic substrate to correlate with clinically serious or life-threatening arrhythmias, mechanical interventions were a logical development. Cobb and co-workers in 1968 reported the first successful surgical division of a bundle of Kent in a patient with intractable arrhythmias.[8] That same year, surgical approaches to the atrioventricular (AV) bundle[9] and the use of pacemakers[10] to treat reciprocating tachycardias were described. Nonsurgical electrical catheter ablation of the AV node was first reported in 1982[11,12] and of accessory pathways in 1984.[13]

As experience with surgical interventions has improved over the past 20 years, success rates in the 95% to 99% range are reported commonly. Because the disorder has potentially life-threatening consequences for otherwise healthy young people, it is imperative that general internists develop an understanding of current management strategies for these patients.

## General Considerations

### *Classification of the Preexcitation Syndromes*

Preexcitation (PR interval <120 milliseconds) results when depolarization of the ventricles occurs prematurely. This requires an accessory pathway composed of either extra myocardial tissue or specialized conducting tissue that permits the wave of depolarization to bypass the delay of the AV node. By convention,[14] accessory pathways are subclassified as accessory connections that insert into myocardium or as bypass tracts that insert into portions of the normal conducting system.

Figure 1 schematically outlines the relative locations of accessory pathways in the various preexcitation syndromes. In the Wolff-Parkinson-White syndrome, the most common form of preexcitation, the accessory pathway is between the atrium and ventricle and hence designated an accessory atrioventricular connection. Mahaim fibers include both nodoventricular (AV node to ventricle) and fasciculoventricular connections (bundle of His to ventricle). Examples of bypass tracts include atriofascicular pathways (which account for some cases of the Long-Ganong-Levine syndrome) and atrionodal pathways (intranodal fibers or James fibers). All accessory pathways potentially can participate in the pathogenesis of arrhythmias.

From the Division of Cardiology, Department of Medicine, Oregon Health Sciences University School of Medicine, Portland.

Reprint requests to Andrew Arai, MD, Division of Cardiology, L462, Department of Medicine, Oregon Health Sciences University, 3181 SW Sam Jackson Park Rd, Portland, OR 97201-3098.

ABBREVIATIONS USED IN TEXT

AV = atrioventricular
ECG = electrocardiogram
EP = electrophysiologic
PSVT = paroxysmal supraventricular tachycardia

*Electrocardiographic Manifestations of the Wolff-Parkinson-White Syndrome*

Although the rest of this article focuses specifically on the Wolff-Parkinson-White syndrome, the concepts that will be developed can be generalized to analyze any of the other forms of preexcitation. Understanding the formation of the components of the electrocardiogram (ECG) resulting from preexcitation provides a logical framework to approach the pathophysiology of arrhythmias seen with the syndrome.[15] In these patients, formation of the QRS complex represents a fusion of electrical activity associated with ventricular depolarization initiated through the accessory AV connection and ventricular depolarization through the normal conducting system. A depolarization originating at the sinus node spreads toward the AV node and the accessory connection (Figure 2-A). Normally, conduction through the AV node is slow, leading to a PR interval between 120 and 200 milliseconds. Because there is no similar delay through the accessory connection, the portion of the ventricle served by the accessory connection depolarizes before the portion depolarized through the bundle of His. This early depolarization of a portion of the ventricle (in a distribution different from that initiated through the bundle of His) results in a short PR interval, the delta wave, and a prolonged QRS duration.

The degree of abnormality seen in the ECG is determined by a number of factors[14]: location of the accessory connection, the site of atrial impulse formation, atrial size, transmission characteristics of the AV node, and transmission characteristics of the accessory connection. In short, the larger the volume of ventricle depolarized through the accessory connection and the earlier this depolarization occurs, the more abnormal the ECG appears (Figure 3). Many patients with this syndrome have minimal preexcitation during sinus rhythm and may have only subtle abnormalities on ECG. Finally, concealed accessory pathways only conduct from ventricle to atrium and hence never exhibit preexcitation during sinus rhythm but still can participate in the pathogenesis of arrhythmias. Table 1 lists several electrocardiographic clues to the presence of the Wolff-Parkinson-White syndrome.[16,17]

TABLE 1.—*Electrocardiographic Clues to the Presence of the Wolff-Parkinson-White Syndrome*

| |
|---|
| PR interval <120 ms* |
| PR interval may be >120 ms in many cases† |
| PR interval will usually be shortest before largest delta wave |
| QRS duration >120 ms* |
| QRS duration may be <120 ms in many cases |
| Delta waves (positive or negative deflections on early portion of QRS complex)*† |
| Delta waves may disappear with reciprocating tachycardia‡ |
| Tall R waves in leads $V_1$ and $V_2$ |
| Differential diagnosis includes right bundle branch block, right ventricular hypertrophy, and posterior infarction† |
| Tachycardias with ventricular response >200 beats/min |
| Atrial fibrillation with very rapid ventricular response (also could represent quinidine effect without digoxin) |
| Atrial fibrillation with intermittent preexcitation§ |

*See Figure 3, ECG 2.
†See Figure 3, ECG 1.
‡See Figure 5, ECG 3 and ECG 4.
§See Figure 6, ECG 6.

*Localization of Accessory Pathways*

Localization of accessory connections becomes essential when considering any nonpharmacologic intervention for this syndrome. Although direct epicardial mapping during surgical intervention and catheter mapping of the retrograde sequence of atrial activation during ventricular pacing or during reciprocating tachycardia remain the best methods of localizing accessory pathways, less invasive testing can provide important information.[18] A knowledge of ECG criteria can increase the recognition of preexcitation, which often

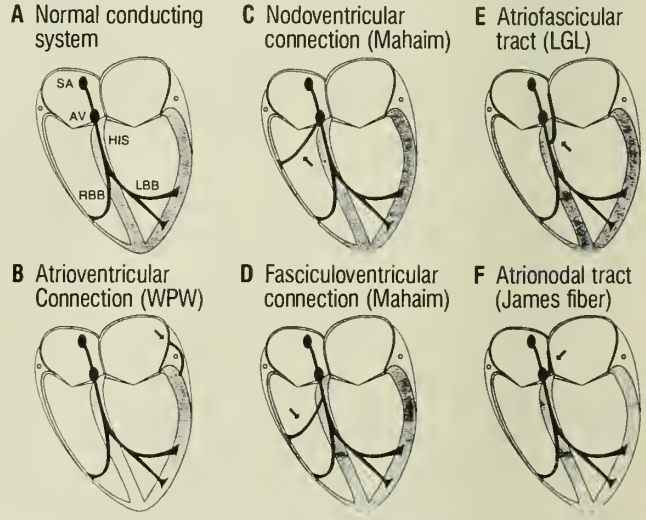



**Figure 1.**—The locations of accessory pathways in the preexcitation syndromes are shown. The components of the normal conducting system are shown in **A.** The arrows designate the accessory pathway in each of the remaining panels (not the direction of conduction). AV = atrioventricular node, HIS = bundle of His, LBB = left bundle branch, LGL = the Long-Ganong-Levine syndrome, RBB = right bundle branch, SA = sinus node, WPW = the Wolff-Parkinson-White syndrome

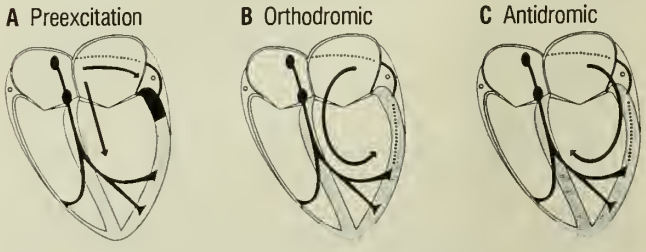



**Figure 2.**—The schematics show the major mechanisms of tachycardias associated with the Wolff-Parkinson-White syndrome. The arrows indicate the direction of electrical conduction. **A,** Preexcitation implies ventricular depolarization through both the normal conducting system and the accessory atrioventricular connection. As described in the text, this helps explain the electrocardiographic abnormalities seen with the Wolff-Parkinson-White syndrome and degeneration of atrial fibrillation to ventricular fibrillation. **B,** The conducting circuit of an orthodromic reciprocating tachycardia involves antegrade conduction along the bundle of His, ventricular depolarization, retrograde conduction along the accessory pathway, and atrial depolarization leading to another cycle. **C,** An antidromic tachycardia involves the same circuit as an orthodromic tachycardia except in the opposite sequence (adapted from Wellens et al[15]).

mimics other electrocardiographic diagnoses such as myocardial infarction or bundle branch block. Furthermore, discordance between localization by different methods suggests either an error in localization or the presence of more than one pathway.

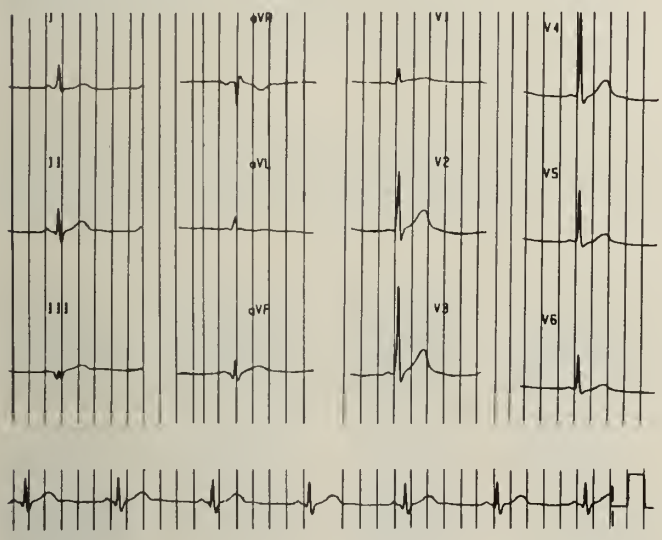
The classification of Rosenbaum and colleagues of type A and type B patterns of preexcitation,[19] although commonly used, is no longer adequate to influence clinical decision making. Useful algorithms can localize the accessory pathway to at least one of four major zones around the heart at the level of the anulus fibrosus: the left free wall, right free wall, anteroseptal, and posteroseptal. Using a standard 12-lead ECG during sinus rhythm, the methods of Lindsay and associates and of Milstein and co-workers are both capable of correctly localizing the accessory pathway in about 90% of cases.[20,21] Table 2 summarizes the Lindsay algorithm, and Figure 4 illustrates the subdivisions of this classification scheme.

Alternative noninvasive techniques for localizing accessory pathways have been described and may play a role in the future. Body surface ECG mapping[22] correctly localizes the pathway in 88% of cases. An analysis of ventricular contraction patterns by digital continuous loop two-dimensional echocardiography[23] and phase-image analysis of radionuclide ventriculography (computerized analysis of ventricular relaxation and contraction)[24] identify the site of accessory pathways in 86% and 88% of cases, respectively. Phase-image analysis has noninvasively localized accessory pathways in patients with equivocal localization during electrophysiologic testing.[25]

The relative frequency of pathways in each zone varies considerably from series to series. Cox and associates have reported 58% left free wall, 24% posteroseptal, 13% right free wall, and 5% anteroseptal pathways in a series of 118 surgical candidates.[26] More than one pathway is found in between 15% and 20% of patients.[26,27]

A number of cardiac anomalies occur in conjunction with accessory pathways. Approximately 5% to 7% of patients

ECG 1




ECG 2

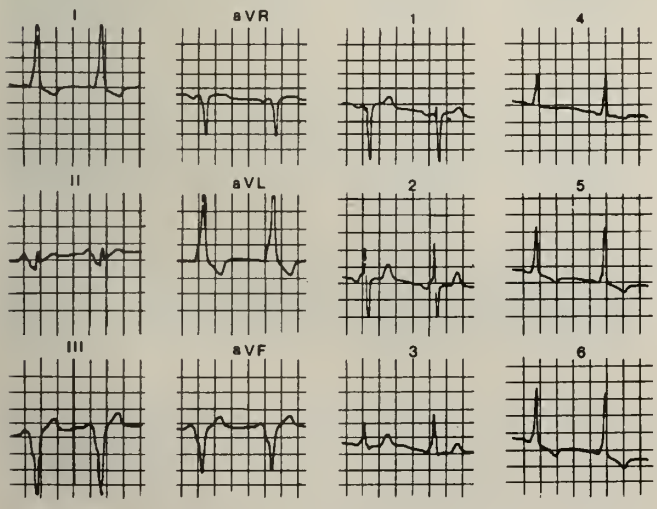



**Figure 3.**—The electrocardiographic (ECG) strips depict the variable expression of preexcitation during sinus rhythm. **ECG 1,** A pseudoinfarction pattern is shown: small q waves in leads III and aVF with R greater than S in $V_1$, which actually represent delta waves from a small area of ventricular preexcitation from a left-sided atrioventricular connection subsequently confirmed by electrophysiologic testing. **ECG 2,** All the classic findings of the Wolff-Parkinson-White syndrome are seen: PR interval less than 120 milliseconds, QRS duration greater than 120 milliseconds, and delta waves in multiple leads.

TABLE 2.—*Electrocardiographic (ECG) Algorithm for Localizing an Accessory Atrioventricular Pathway**

| *Region* | *ECG Leads With a Negative Delta Wave* | *QRS Axis in the Frontal Plane, ms* | *Frontal Lead With R > S* |
|---|---|---|---|
| I Left lateral . . . . . | I and/or aVL | Normal | $V_1$ through $V_3$ |
| II Left posterior . . . . | III and aVF | −75 to +75 | $V_1$ |
| III Posteroseptal . . . . | III and aVF | 0 to −90 | $V_2$ through $V_4$ |
| IV Right free wall . . . | aVR | Normal | $V_3$ through $V_5$ |
| V Anteroseptal . . . . | $V_1$ and $V_2$ | Normal | $V_3$ through $V_5$ |

*From Lindsay et al.[20]

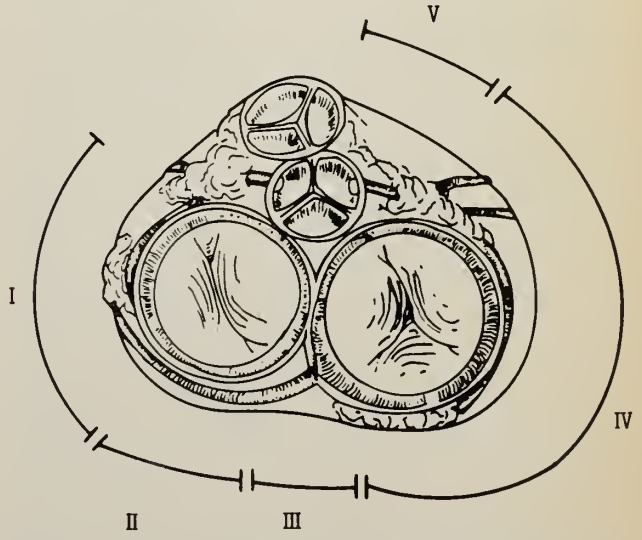



**Figure 4.**—The cross-sectional diagram of the heart shows the anatomic regions differentiated by the Lindsay criteria. The cross section is at the level of the anulus fibrosus, which divides the atria from the ventricles: **region I,** the lateral free wall of the left ventricle; **region II,** the left posterior free wall; **region III,** the posteroseptal and posterior paraseptal regions; **region IV,** the right free wall; and **region V,** the anteroseptal or right anterior paraseptal region (from Lindsay et al[20]).

with the Wolff-Parkinson-White syndrome have Ebstein's anomaly associated with multiple right-sided pathways. Other disorders associated with this syndrome include transposition of the great arteries, tricuspid atresia, endocardial fibroelastosis, idiopathic hypertrophic subaortic stenosis, and mitral valve prolapse.[28] About 5% of patients with this syndrome have coincident coronary artery disease at the time of operation.[26,29]

*Prevalence of the Wolff-Parkinson-White Syndrome and Patterns of Inheritance*

Vidaillet and colleagues compiled data from 14 major collections of ECGs published between 1940 and 1981.[30] There were 625 cases of preexcitation in a population of 427,639—a prevalence of 0.15%. Considering the variable expression of preexcitation on baseline ECGs and the incidence of concealed accessory pathways, this likely underestimated the true prevalence.

Expanding on this data base, Vidaillet and associates retrospectively identified evidence of preexcitation in 13 first-degree relatives of 383 index patients with the Wolff-Parkinson-White syndrome (3.4%).[30] This was about 20 times the expected rate based on the general prevalence and was most consistent with an autosomal-dominant pattern of inheritance.

It is important to note, however, that most cases are not familial. Clinically, familial cases have a higher frequency of multiple pathways, are not associated with other cardiac abnormalities, and may have a higher frequency of sudden death than sporadic cases.

## Major Arrhythmias Associated With the Wolff-Parkinson-White Syndrome

*Reciprocating Tachycardia (Reentry Tachycardias)*

The major mechanisms of tachycardias seen with the Wolff-Parkinson-White syndrome are illustrated in Figure 2. A reciprocating tachycardia[31] is initiated when a critically timed premature atrial contraction or premature ventricular contraction cannot be conducted down one pathway but can be conducted down the other (unidirectional block). An orthodromic tachycardia is established when conduction goes from the atria antegrade through the AV node and the bundle of His to the ventricles and returns to the atria retrograde through the accessory pathway (Figure 2-B). The arrhythmia is sustained by continued reciprocation around this closed loop. The resulting tachycardia generally has a narrow QRS complex because the ventricles are depolarized through the bundle of His. Orthodromic reciprocating tachycardia is the most common tachycardia associated with this syndrome and is the mechanism underlying about 20% of cases of paroxysmal supraventricular tachycardia (PSVT) (Figure 5).

Antidromic tachycardias occur perhaps a tenth as often as orthodromic tachycardias.[15] An antidromic tachycardia uses the same circuit, but conduction travels in the opposite direction (antegrade through the accessory pathway and retrograde through the bundle of His, Figure 2-C). Because depolarization of the ventricles is not initiated through the bundle of His, the tachycardia is a wide complex rhythm (Figure 6, ECG 5) that must be differentiated from ventricular tachycardia.

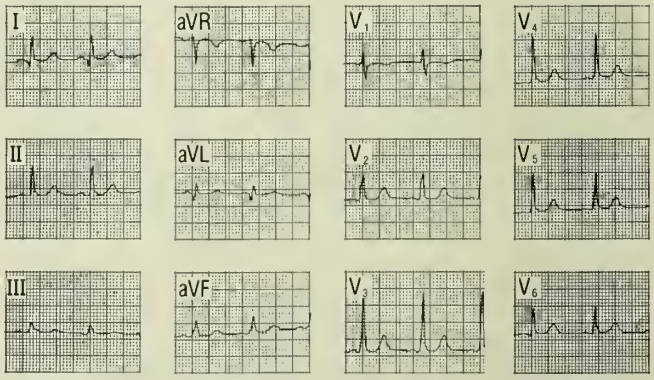
Other regular wide complex tachycardias with a 1:1 atrial to ventricular relationship that have been recorded in patients with the Wolff-Parkinson-White syndrome include slow atrial flutter or ectopic atrial tachycardia with 1:1 conduction through the accessory pathway, multiple accessory pathway mechanisms using antidromic conduction, and reentry over an associated Mahaim fiber (suggested by a left bundle branch block morphology, left axis deviation, and the response to AV nodal blocking agents).[32] Finally, an orthodromic PSVT with rate-related bundle branch block is a common cause of a regular wide complex tachycardia in patients with this syndrome.

The presence of multiple accessory pathways allows a number of variations of reciprocating tachycardias. Any two atrioventricular connections—including a combination of two accessory pathways or a combination of an accessory pathway and the normal conducting system—can form a closed atrioventricular loop capable of sustaining a reciprocating tachycardia. In a particular patient, the components of the closed atrioventricular loop can vary with different tachycardias and even on a beat-to-beat basis.

*Atrial Fibrillation*

Atrial fibrillation occurs in 11.5% to 39% of patients with the Wolff-Parkinson-White syndrome.[32] Why these patients are more susceptible to atrial fibrillation is unknown. The accessory pathway must play an important role in the devel-

ECG 3




ECG 4

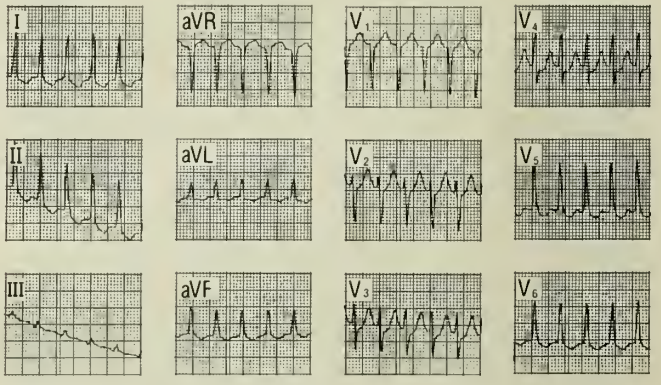



**Figure 5.**—Orthodromic tachycardia (ECG 4) is compared with normal sinus rhythm and preexcitation (ECG 3). **ECG 3,** During sinus rhythm, this patient has an abnormal R-wave progression across the precordial leads and q waves in leads I and aVL, which represent preexcitation from a left free wall pathway confirmed by electrophysiologic testing. **ECG 4,** During her orthodromic tachycardia (paroxysmal supraventricular tachycardia [PSVT]), all conduction along the accessory pathway is from the ventricle to the atrium, so all evidence of preexcitation disappears. Thus, the q waves and R-wave progression return to normal during her PSVT.

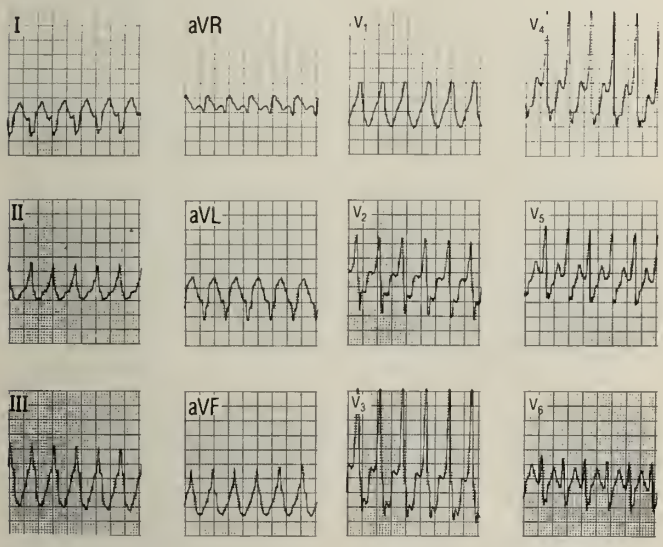
opment of atrial fibrillation because surgical ablation of the pathway usually eliminates further episodes of this arrhythmia in the absence of other predisposing factors.[33,34] Retrograde conduction of premature ventricular beats may arrive at a time of atrial vulnerability to fibrillation or, in combination with a sinus beat, cause nonuniform depolarization of the atria resulting in fibrillation.[32] Atrial fibrillation with a rapid ventricular response and intermittent wide complex beats (Figure 6, ECG 6) is highly suggestive of the syndrome but needs to be differentiated from premature ventricular complexes and rate-related bundle branch blocks (Ashman's phenomena).

*Ventricular Fibrillation*

The incidence of ventricular fibrillation and sudden death in patients with the Wolff-Parkinson-White syndrome remains the single most important stimulus for clinical evaluation and aggressive treatment modalities. Although the incidence of ventricular fibrillation among these patients has been reported to be as high as 11%,[32] this likely represents referral center bias, and the actual incidence is probably much lower.

The pattern of conduction through a heart with an accessory pathway helps describe one potential mechanism for ventricular fibrillation developing from atrial fibrillation (Figure 2-A). Normally the ventricular response to atrial fibrillation is limited by the refractory period of the AV node. An accessory pathway bypasses the protective mechanism of the AV node. An accessory pathway with a relatively short effective refractory period can allow a rapid ventricular response to atrial fibrillation. This rapid ventricular response may degenerate to ventricular fibrillation. Alternatively, rapid conduction through the accessory pathway may allow stimulation of the ventricle during a period of ventricular susceptibility to fibrillation.[10]

ECG 5




ECG 6

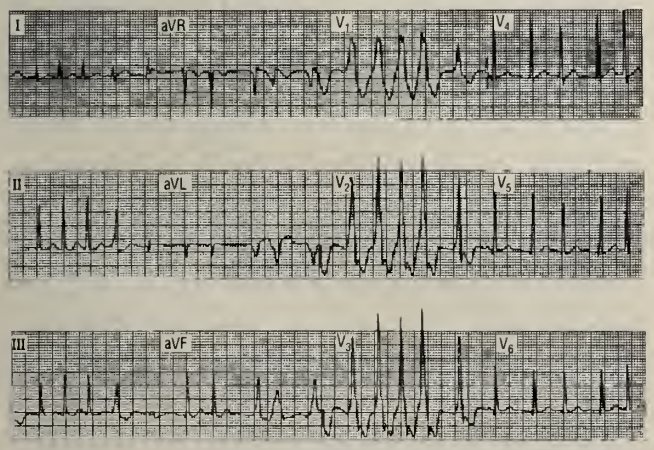



**Figure 6.**—Antidromic tachycardia (ECG 5) is compared with atrial fibrillation with intermittent preexcitation (ECG 6) in the same patient. **ECG 5,** Antidromic tachycardia is a regular wide-complex tachycardia difficult to distinguish from ventricular tachycardia. The p waves following the QRS complex in lead $V_4$ suggest a 1:1 atrioventricular relationship and are compatible with a reciprocating tachycardia. **ECG 6,** Note also that the intermittent preexcited (wide complex) beats during atrial fibrillation have similar axis and morphology to the antidromic tachycardia. This patient has a left-sided accessory pathway confirmed by electrophysiologic testing.

*Asymptomatic Patients With the Syndrome*

Although the natural history of the Wolff-Parkinson-White syndrome suggests a benign prognosis for asymptomatic patients, many patients have presented with sudden cardiac death.[32] Electrophysiologic (EP) testing in 42 asymptomatic patients with the syndrome revealed potentially lethal accessory pathway characteristics in 17% to 21% (as indicated by a minimum cycle length of less than 250 milliseconds during induced atrial fibrillation or an antegrade effective refractory period of less than 270 milliseconds, respectively).[35] This group of patients remained asymptomatic during an average 29-month follow-up. Intriguingly, one patient not included in the study died suddenly after enrollment but before EP testing. During longitudinal EP testing of 29 of these patients, 31% lost the capacity for preexcitation. These findings further support a benign prognosis for asymptomatic patients,[36] but the appropriate evaluation and treatment of asymptomatic patients with the Wolff-Parkinson-White syndrome remains an area of great controversy.

## EP Testing and Noninvasive Testing to Predict Risk of Sudden Cardiac Death in the Wolff-Parkinson-White Syndrome

Electrophysiologic testing can provide useful information in a patient with the Wolff-Parkinson-White syndrome, including the confirmation of preexcitation, characterization of associated tachycardias, localization of the accessory pathway, characterization of the accessory pathway functional behavior, and the determination of drug effects in individual patients.[32] Two major EP criteria are used in determining an increased risk of sudden death: the shortest interval between preexcited beats during atrial fibrillation (shortest RR interval <250 milliseconds, which is equivalent to a heart rate of 240 per minute),[37] and the antegrade effective refractory period of the accessory pathway (<270 milliseconds).

The most commonly used noninvasive tests are exercise testing[38] and the response to an infusion of antiarrhythmic agents such as procainamide hydrochloride or ajmaline.[39,40] A complete block of conduction down the accessory pathway by either method suggests a low risk of sudden death. Intermittent preexcitation on routine ECG monitoring also suggests a favorable prognosis.

Sharma and co-workers compared electrophysiologic

testing and noninvasive testing as methods for identifying patients with the syndrome at high risk for sudden death.[41] Testing was done on 58 patients including 9 with a previous history of life-threatening arrhythmia. By EP testing, the shortest interval between preexcited beats was the best predictor of sudden death. The sensitivity of EP testing in predicting sudden death was 87.5%. Continuous preexcitation following a disopyramide infusion or during an exercise test was a slightly less sensitive predictor of sudden death (71.4% sensitivity and 80% sensitivity, respectively). All three methods were found to have low specificity and hence a poor positive predictive value because the overall incidence of sudden death in this syndrome is low (Bayesian analysis).

If the findings of EP testing were used to recommend surgical therapy for this group of patients, 1 of 8 patients with a risk of sudden death would be missed and 30 of 58 patients with a benign course would be inappropriately treated. The noninvasive tests would do less well, and sequential testing would add only a marginal improvement in predictive value.

Other groups have reported false-negative tests,[42,43] which support the findings of Sharma and colleagues. Currently accepted indications for EP testing[44,45] are listed in Table 3.

TABLE 3.—*Indications for Electrophysiologic Testing in Patients With the Wolff-Parkinson-White Syndrome*

| |
|---|
| Ventricular fibrillation or sudden death |
| Syncope |
| Atrial fibrillation or flutter with rapid ventricular response |
| Wide complex tachycardia |
| Symptomatic arrhythmias |
| Supraventricular tachycardia refractory to class 1A antiarrhythmic agents |
| Localization of pathway before cardiac operation or catheter ablation |

## Medical Management of Arrhythmias Associated With the Wolff-Parkinson-White Syndrome

Medical management encompasses the treatment of acute arrhythmias, prophylaxis to diminish the incidence of recurrent arrhythmias, and prophylaxis against ventricular fibrillation. Before addressing these goals, we will review some pharmacologic considerations peculiar to accessory pathways. Pharmacologic effects on any one or more of the components of the circuit used by a reciprocating tachycardia potentially can abolish an acute arrhythmia or diminish the likelihood of recurrence. The prevention of ventricular fibrillation hinges on the ability to prevent a rapid ventricular response to atrial fibrillation and hence depends on blocking or slowing conduction through the accessory pathway.

Human variability has made the prediction of pharmacologic effects in any given patient difficult. The use of digoxin clearly has been associated with precipitating ventricular fibrillation in many patients with the Wolff-Parkinson-White syndrome.[46] The use of digitalis increases the ventricular response to atrial fibrillation in about a third of patients but has no effect or slows the ventricular response in the other two thirds. Electrophysiologic testing can differentiate those patients at high risk from those at low risk for ventricular fibrillation developing with the use of digitalis. Its use should be avoided in a patient with this syndrome unless EP testing has been done and has verified the safety of therapy.

Similarly, the intravenous administration of verapamil has been implicated as precipitating ventricular fibrillation in patients with this syndrome treated for supraventricular tachycardias.[47] As with digoxin, giving verapamil can cause acceleration or deceleration of conduction within the accessory pathway. Verapamil also has important hemodynamic effects and may lower the fibrillation threshold. Electrophysiologic testing should be done before initiating therapy with this drug.[48]

Wellens and associates described another idiosyncratic pharmacologic phenomenon that should be considered when evaluating the efficacy of antiarrhythmic therapy in patients with the Wolff-Parkinson-White syndrome.[49] While testing the use of procainamide hydrochloride, ajmaline, and quinidine in these patients, they noted that accessory pathways with a short effective refractory period (<270 milliseconds) were substantially less responsive to therapy than those with a longer effective refractory period. Thus, those at highest risk for a rapid ventricular response to atrial fibrillation were least likely to be protected by antiarrhythmic agents. This also emphasized the importance of evaluating the efficacy of therapy on groups of patients with accessory pathways exhibiting short effective refractory periods. Finally, they noted different effects of these agents on antegrade and retrograde conduction potentially resulting in a proarrhythmia.

Administering isoproterenol hydrochloride, and presumably states of increased sympathetic tone, can overcome the protective benefits of antiarrhythmic pharmacologic therapy in some patients. Routine exercise treadmill testing after attaining a therapeutic dose may help reveal therapeutic failures missed by EP testing done at rest.

The approach to specific arrhythmias can be flexible and depends greatly on the frequency and severity of the arrhythmias in an individual patient (Table 4). Reciprocating tachycardias using an accessory pathway and the AV node often resolve with vagal maneuvers; Valsalva's maneuver in the supine position appears to be the most effective.[50] This may be the only therapy necessary for a young, healthy, minimally symptomatic patient. More severe or refractory reciprocating tachycardias should be treated in a carefully monitored setting with the capability of cardiopulmonary resuscitation because of the risk of inducing more malignant arrhythmias. A graded approach might progress from verapamil use (with continuous electrocardiographic monitoring) to that of procainamide to overdrive pacing or DC cardioversion. Although $\beta$-blockers likely have little role in acute arrhythmias associated with the Wolff-Parkinson-White syndrome, their use may help prevent arrhythmias requiring increased sympathetic tone for initiating or maintaining the arrhythmia.[51] Preventive therapy with a class 1A antiarrhythmic agent often helps.[48] Although the class 1C agents encainide hydrochloride[52] and flecainide acetate have been shown to be effective and well-tolerated drugs for treating arrhythmias associated with the syndrome, neither drug currently is approved by the Food and Drug Administration for these indications. The possible proarrhythmic effects of class 1C agents in patients after a myocardial infarction studied in the Cardiac Arrhythmia Suppression Trial (CAST) may be difficult to extrapolate to patients with the Wolff-Parkinson-White syndrome and otherwise healthy myocardium but warrant consideration of other treatments first.[53] The efficacy of amiodarone is excellent,[54] but because of its toxic side effects, its use should be reserved for exceptionally refractory patients who

are not surgical candidates. Investigational agents that may soon be available include injectable diltiazem hydrochloride,[55] propafenone,[56,57] sotalol hydrochloride,[58] and adenosine phosphate.[59]

Atrial fibrillation with a rapid ventricular response in patients with this syndrome presents a particular challenge to clinicians. One important clue to the diagnosis of the syndrome is the presence of intermittent preexcited beats (Figure 6, ECG 6). The use of digoxin or verapamil is contraindicated in these patients unless previously documented safe by EP testing. The acute management is DC cardioversion if a patient is hemodynamically unstable and the use of procainamide or possibly lidocaine for more stable patients. Prophylactic therapy again includes class 1A agents, amiodarone, and possibly class 1C agents. Any patient with the Wolff-Parkinson-White syndrome surviving an episode of atrial fibrillation with rapid ventricular response degenerating to ventricular fibrillation should be considered a candidate for nonpharmacologic therapy.

## Nonpharmacologic Therapy

Surgical ablation of accessory pathways, by either an epicardial or an endocardial approach, remains the most widely accepted nonpharmacologic therapy available for patients with the Wolff-Parkinson-White syndrome. Catheter ablation of pathways is developing into a more generally applicable technique, but only a limited number of patients have been treated by this modality. Pacemakers have been used to treat symptomatic arrhythmias but are less favored because they offer no protection from a rapid ventricular response to atrial fibrillation. Indications for ablation procedures are listed in Table 5.

### *Surgical Ablation of Accessory Pathways*

The accessory pathway can be localized to various segments of the anulus fibrosus as described previously. Within a given zone, the accessory pathway can be located anywhere between the endocardium and the epicardium, as illustrated in Figure 7-A. The endocardial approaches vary somewhat depending on the location of the pathway but generally involve an atriotomy and dissection of the atrioventricular junction from the endocardial surface out to the epicardial surface. Interruption of the atrioventricular conduction is accomplished through damage either to the atrial or to the ventricular insertions of the accessory pathway (Figure 7-B). The epicardial approach begins with dissection of the atrioventricular junction from the epicardial surface, destroying possible epicardial pathways at the atrial origin. An atriotomy is avoided by cryosurgical ablation of any remaining endocardial accessory connections (Figure 7-C).

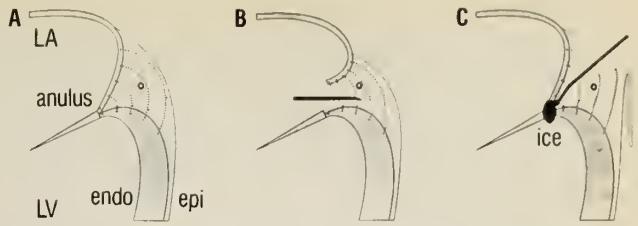



**Figure 7.**—The diagrams show surgical ablation of atrioventricular connections. **Panel A,** The anatomy of the atrioventricular junction is illustrated. The dotted lines represent possible locations for accessory atrioventricular connections. **Panel B,** The endocardial surgical approach usually involves dissecting the ventricular insertion of the accessory pathway. **Panel C,** The epicardial approach begins at the epicardial surface with dissection of the atrial origins of the accessory pathway. The pathways close to the endocardial surface are then cryosurgically ablated as indicated by the patch of "ice" (adapted from JAMA 1987; 258:385). anulus = area of the anulus fibrosus, endo = endocardial surface, epi = epicardial surface, LA = left atrium, LV = left ventricle

Cox has favored an endocardial dissection because he noted hemorrhagic complications from the friable epicardial peel and lower success rates during epicardial approaches.[60] Cox has reported successful endocardial surgical ablation of 148 of a total 149 accessory pathways between 1980 and 1985. The operative mortality for elective cases in the absence of other cardiac anomalies is about 0.8%.[32]

Fischell and associates reported similar success rates with no mortality in a group of 41 patients undergoing endocardial ablation of accessory pathways. At follow-up three years later, 98% of patients were free of preexcitation-related arrhythmias. Hospital admissions for arrhythmia were reduced by a factor of 10, and 12 of 13 patients previously unable to work because of arrhythmias returned to work.[61]

Guiraudon and colleagues[62] and Bredikis and co-workers[63,64] have been major proponents for the epicardial cryosurgical ablation of accessory pathways. Epicardial approaches allow continuous electrocardiographic monitoring of the accessory pathway during the procedure, avoid damage to the AV node, and in many patients can eliminate the need for cardiopulmonary bypass.

In a series of 105 patients with accessory pathways, 104 underwent successful epicardial cryosurgical ablation of accessory pathways and were free of arrhythmias at 18-month follow-up. Four patients required a second operation, and one patient required three operations.[65] Similarly, all 13 patients with a posteroseptal pathway had successful epicardial ablation without complications of AV block or recurrent arrhythmias.[66]

TABLE 4.—*Medical Management of Arrhythmias Associated With the Wolff-Parkinson-White Syndrome*

| *Acute Management* | *Prophylactic Treatment* |
|---|---|
| *Reciprocating Tachycardias* | |
| Vagal maneuvers | Class 1A agents |
| Verapamil (ECG monitored) | β-Blockers |
| Procainamide hydrochloride | Verapamil |
| Overdrive pacemaker | Class 1C agents (see text) |
| Electrical cardioversion | Amiodarone |
| *Atrial Fibrillation* | |
| Procainamide hydrochloride | Class 1A agents |
| Electrical cardioversion | Class 1C agents (see text) |
| | Amiodarone |

ECG = electrocardiographically

TABLE 5.—*Indications for Surgical Ablation of Accessory Pathways in the Wolff-Parkinson-White Syndrome*

History of life-threatening arrhythmia
High risk of sudden death
Arrhythmias refractory to medical therapy
Intolerance to drug therapy or detrimental side effects
Other cardiac defect requiring a cardiac operation
Elective alternative to lifelong drug therapy

Although proponents of endocardial and epicardial approaches have remarkable success rates, the epicardial approach may be more difficult and have a longer learning curve. The reported success rates of 95% to 100% represent those of the most experienced centers, and the rates are likely to be somewhat lower at other centers still gaining experience.

### *Catheter Ablation of Accessory Pathways*

Catheters carefully positioned adjacent to the accessory pathway can deliver sufficient electrical or radio-frequency energy to ablate the pathway permanently. Initial rates of 75% success in ablating posteroseptal pathways by a catheter placed at the os of the coronary sinus have encouraged further experimentation.[67] Catheter positioning on the internal surface of the right or left atrioventricular anulus has allowed catheter ablation of accessory pathways in any distribution.[68] In their series of 35 patients, Warin and associates reported successful catheter ablation of the accessory pathway in 32 cases. Complications were generally benign except for one patient with a posteroseptal pathway who suffered complete heart block. In a more recent series, in about two thirds of patients the posteroseptal pathways were successfully ablated.[69] Using radio-frequency energy, catheter ablation has been safely done of some accessory pathways[70-72] and the AV node in several patients with refractory paroxysmal supraventricular tachycardia.[73]

The major limitations of catheter ablation techniques have been lower overall success rates than with surgical procedures and some serious complications. Electrical catheter ablation within the coronary sinus has caused myocardial infarctions in some patients and ruptured the coronary sinus resulting in cardiac tamponade in others.[74] Although catheter ablation techniques remain investigational modes of therapy,[75,76] recent developments have extended the range of accessible pathways and the safety of the procedure. The prospect of permanently ablating the accessory pathway without requiring a cardiac operation remains a driving force motivating this research. Radio-frequency energy may allow permanent catheter ablation of accessory pathways without requiring general anesthesia. These techniques hold great promise for the near future.

### *Other Nonpharmacologic Therapy for the Wolff-Parkinson-White Syndrome*

The use of pacemakers to terminate reciprocating tachycardia was first described in 1968.[77] Just as critically timed premature beats can initiate a reciprocating tachycardia, they may also terminate a tachycardia if timed appropriately. Although this mode of therapy is capable of terminating symptomatic PSVT, it does not alter the incidence of the tachycardia and, most importantly, does not protect a patient from the development of a rapid ventricular response to atrial fibrillation or sudden death.[78] Furthermore, antitachycardia pacemakers can induce atrial fibrillation in patients with this syndrome and thus should not be implanted in patients who have short antegrade effective refractory periods.[79]

Finally, left thoracic sympathectomy has been reported to abolish recurrent PSVT in two patients with the Wolff-Parkinson-White syndrome and evidence of increased left sympathetic tone.[80] While ablation procedures are accepted modes of therapy, sympathectomy must be considered investigational.

## REFERENCES


1. Wilson FN: A case in which the vagus influenced the form of the ventricular complex of the electrocardiogram. Arch Intern Med 1915; 16:1008-1027

2. Wolff L, Parkinson J, White PD: Bundle branch block with short PR interval in healthy young people prone to paroxysmal tachycardia. Am Heart J 1930; 5:685-704

3. Wolferth CC, Wood FC: Mechanism of production of short PR intervals and prolonged QRS complexes in patients with presumably undamaged hearts: Hypothesis of accessory pathway of auriculo-ventricular conduction (bundle of Kent). Am Heart J 1933; 8:297

4. Wood FC, Wolferth CC, Geckeler GD: Histologic demonstration of accessory muscular connections between auricle and ventricle in a case of short PR interval and prolonged QRS complex. Am Heart J 1943; 25:454-462

5. Schwartz SP, Jezer A: Studies on transient ventricular fibrillation—Observations on the alterations in the rhythm of the heart preceding syncopal seizures in a patient with normal sinus rhythm. Am J Med Sci 1934; 187:469

6. Dreifus LS, Haiat R, Watanabe Y, et al: Ventricular fibrillation—A possible mechanism of sudden death in patients with Wolff-Parkinson-White syndrome. Circulation 1971; 42:520-527

7. Durrer D, Roos JP: Epicardial excitation of the ventricles in a patient with Wolff-Parkinson-White syndrome (type B). Circulation 1967; 35:15-21

8. Cobb FR, Blumenschein SD, Sealy WC, et al: Successful surgical interruption of the bundle of Kent in a patient with Wolff-Parkinson-White syndrome. Circulation 1968; 38:1018-1029

9. Dreifus LS, Nichols H, Morse D, et al: Control of recurrent tachycardia of Wolff-Parkinson-White syndrome by surgical ligature of the A-V bundle. Circulation 1968; 38:1030-1036

10. Ryan GF, Easley RM, Zaroff LI, et al: Paradoxical use of a demand pacemaker in treatment of supraventricular tachycardia due to the Wolff-Parkinson-White syndrome. Circulation 1968; 38:1037-1043

11. Gallagher JJ, Svenson RH, Kasell JH, et al: Catheter technique for closed chest ablation of the atrioventricular conduction system. N Engl J Med 1982; 306:194-200

12. Scheinman MM, Morady F, Hess DS, et al: Catheter-induced ablation of the atrioventricular junction to control refractory supraventricular arrhythmias. JAMA 1982; 248:851-855

13. Morady F, Scheinman MM: Transvenous catheter ablation of a posteroseptal accessory pathway in a patient with the Wolff-Parkinson-White syndrome. N Engl J Med 1984; 310:705-707

14. Anderson RH, Becker AE, Brechenmacher C, et al: Ventricular preexcitation—A proposed nomenclature for its substrates. Eur J Cardiol 1975; 3:27-36

15. Wellens HJJ, Brugada P, Penn OC: The management of preexcitation syndromes. JAMA 1987; 257:2325-2333

16. Richardson JM: Ventricular preexcitation—Practical considerations. Arch Intern Med 1983; 143:760-764

17. Kay GN, Pressley JC, Packer DL, et al: Value of the 12-lead ECG in discriminating atrioventricular nodal reciprocating tachycardia from circus movement atrioventricular tachycardia utilizing a retrograde accessory pathway. Am J Cardiol 1987; 59:296-300

18. Gallagher JJ: Localization of accessory atrioventricular pathways: What's the 'gold standard?' (Editorial). PACE 1987; 10:583-584

19. Rosenbaum FF, Hecht HH, Wilson FN, et al: The potential variations of the thorax and esophagus in anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome). Am Heart J 1945; 29:289-326

20. Lindsay BD, Crossen KJ, Cain ME: Concordance of distinguishing electrocardiographic features during sinus rhythm with the location of accessory pathways in the Wolff-Parkinson-White syndrome. Am J Cardiol 1987; 59:1093-1102

21. Milstein S, Sharma AD, Guiraudon GM, et al: An algorithm for the electrocardiographic localization of accessory pathways in the Wolff-Parkinson-White syndrome. PACE 1987; 10:555-563

22. Kamakura S, Shimomura K, Ohe T, et al: The role of initial minimum potentials on body surface maps in predicting the site of accessory pathways in patients with Wolff-Parkinson-White syndrome. Circulation 1986; 74:89-96

23. Windle JR, Armstrong WF, Feigenbaum H, et al: Determination of the earliest site of ventricular activation in Wolff-Parkinson-White syndrome: Application of digital continuous loop two-dimensional echocardiography. J Am Coll Cardiol 1986; 7:1286-1294

24. Botvinick E, Frais M, O'Connell W, et al: Phase image analysis of patients with ventricular pre-excitation syndromes. J Am Coll Cardiol 1984; 3:799-814

25. Johnson LL, Seldin DW, Hsiao-Lin Y, et al: Phase analysis of gated blood pool scintigraphic images to localize bypass tracts in WPW syndrome. J Am Coll Cardiol 1986; 8:67-75

26. Cox JL, Gallagher JJ, Cain ME: Experience with 118 consecutive patients undergoing operation for the Wolff-Parkinson-White syndrome. J Thorac Cardiovasc Surg 1985; 90:490-501

27. Gallagher JJ, Sealy WC, Kasell J, et al: Multiple accessory pathways in patients with the pre-excitation syndrome. Circulation 1976; 54:571-591

28. Wellens HJJ, Farre J, Bar FWHM: The Wolff-Parkinson-White syndrome, chap 11, *In* Mandel WJ (Ed): Cardiac Arrhythmias—Their Mechanisms, Diagnosis, and Management, 2nd Ed. Philadelphia, Lippincott, 1987, pp 274-296

29. Fischell TA, Stinson EB, Derby GC, et al: Long term follow-up after surgical correction of Wolff-Parkinson-White syndrome. J Am Coll Cardiol 1987; 9:283-287

30. Vidaillet HJ, Pressley JC, Henke E, et al: Familial occurrence of accessory atrioventricular pathways (preexcitation syndrome). N Engl J Med 1987; 317:65-69

31. Durrer D, Schoo L, Schuilenburg RM, et al: The role of premature beats in the initiation and the termination of supraventricular tachycardia in the Wolff-Parkinson-White syndrome. Circulation 1967; 36:644-662

32. Gallagher JJ, Pritchett EL, Sealy WC, et al: The preexcitation syndromes. Prog Cardiovasc Dis 1978; 20:285-327

33. Waspe LE, Brodman R, Kim SG, et al: Susceptibility to atrial fibrillation and ventricular tachyarrhythmia in the Wolff-Parkinson-White syndrome: Role of the accessory pathway. Am Heart J 1986; 112:1141-1152

34. Sharma AD, Klein GJ, Guiraudon GM, et al: Atrial fibrillation in patients with Wolff-Parkinson-White syndrome: Incidence after surgical ablation of the accessory pathway. Circulation 1985; 72:161-169

35. Milstein S, Sharma AD, Klein GJ: Electrophysiologic profile of asymptomatic Wolff-Parkinson-White syndrome. Am J Cardiol 1986; 57:1097-1100

36. Klein GJ, Yee R, Sharma AD: Longitudinal electrophysiologic assessment of asymptomatic patients with the Wolff-Parkinson-White electrocardiographic pattern. N Engl J Med 1989; 320:1229-1233

37. Klein GJ, Bashorne TM, Sellers TD, et al: Ventricular fibrillation in the Wolff-Parkinson-White syndrome. N Engl J Med 1979; 301:1080-1085

38. Bricker JT, Porter CJ, Garson A Jr, et al: Exercise testing in children with WPW. Am J Cardiol 1985; 55:1001-1004

39. Eshchar Y, Belhassen B, Laniado S: Comparison of exercise and ajmaline tests with electrophysiologic study in the Wolff-Parkinson-White syndrome. Am J Cardiol 1986; 57:782-786

40. Wellens HJJ, Bar FW, Gorgels AP, et al: Use of ajmaline in patients with the Wolff-Parkinson-White syndrome to disclose short refractory period of the accessory pathway. Am J Cardiol 1980; 45:130-133

41. Sharma AD, Yee R, Guiraudon G, et al: Sensitivity and specificity of invasive and noninvasive testing for risk of sudden death in Wolff-Parkinson-White syndrome. J Am Coll Cardiol 1987; 10:373-381

42. Critelli G, Gallagher JJ, Perticone F, et al: Evaluation of noninvasive tests for identifying patients with preexcitation syndrome at risk of rapid ventricular response. Am Heart J 1984; 108(pt 1):905-909

43. Cavalli A, Maggioni A, Tusa M, et al: Two false-negative responses to the ajmaline test in the Wolff-Parkinson-White syndrome. PACE 1985; 8:832-837

44. Rinne C, Klein GJ, Sharma AD, et al: Relation between clinical presentation and induced arrhythmia in the Wolff-Parkinson-White syndrome. Am J Cardiol 1987; 60:576-579

45. Health and Public Policy Committee, American College of Physicians: Diagnostic endocardial electrical recording and stimulation. Ann Intern Med 1984; 100:452-453

46. Sellers TD, Bashore TM, Gallagher JJ: Digitalis in the pre-excitation syndrome. Circulation 1977; 56:260-267

47. McGovern B, Garan H, Ruskin JN: Precipitation of cardiac arrest by verapamil in patients with Wolff-Parkinson-White syndrome. Ann Intern Med 1986; 104:791-794

48. Gulamhusein S, Ko P, Carruthers SG, et al: Acceleration of the ventricular response during atrial fibrillation in the Wolff-Parkinson-White syndrome after verapamil. Circulation 1982; 65:348-354

49. Wellens HJJ, Bar FW, Dassen WRM, et al: Effect of drugs in the Wolff-Parkinson-White syndrome—Importance of initial length of effective refractory period of the accessory pathway. Am J Cardiol 1980; 46:665-669

50. Mehta D, Wafa S, Ward DE, et al: Relative efficacy of various physical manoeuvres in the termination of junctional tachycardia. Lancet 1988; 1:1181-1185

51. Prystowsky EN, Greer S, Packer DL, et al: Beta-blocker therapy for the Wolff-Parkinson-White syndrome. Am J Cardiol 1987 Aug; 60:46D-50D

52. Prystowsky EN, Klein GJ, Rinkenberger RL, et al: Clinical efficacy and electrophysiologic effects of encainide in patients with Wolff-Parkinson-White syndrome. Circulation 1984; 69:278-287

53. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators: Preliminary report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989; 321:406-412

54. Feld GK, Nademanee K, Weiss J, et al: Electrophysiologic basis for the suppression by amiodarone of orthodromic supraventricular tachycardia complicating preexcitation syndromes. J Am Coll Cardiol 1984; 3:1298-1307

55. Shenasa M, Fromer M, Faugere G, et al: Efficacy and safety of intravenous and oral diltiazem for Wolff-Parkinson-White syndrome. Am J Cardiol 1987; 59:301-306

56. Ludmer PL, McGowan NE, Antman EM, et al: Efficacy of propafenone in Wolff-Parkinson-White syndrome: Electrocardiographic findings and long term follow-up. J Am Coll Cardiol 1987; 9:1357-1363

57. Breithardt G, Borggrefe M, Wiebringhaus E, et al: Effect of propafenone in the Wolff-Parkinson-White syndrome: Electrophysiologic findings and long term follow-up. Am J Cardiol 1984; 54:29D-39D

58. Kunze KP, Schluter M, Kuck KH: Sotalol in patients with Wolff-Parkinson-White syndrome. Circulation 1987; 75:1050-1057

59. Overholt DO, Rheuban KS, Gutgesell HP, et al: Usefulness of adenosine for arrhythmias in infants and children. Am J Cardiol 1988; 61:336-340

60. Cox JL: The status of surgery for cardiac arrhythmias. Circulation 1985; 71:413-417

61. Fischell TA, Stinson EB, Derby GC, et al: Long-term follow-up after surgical correction of Wolff-Parkinson-White syndrome. J Am Coll Cardiol 1987; 9:283-287

62. Guiraudon GM, Klein GJ, Sharma AD, et al: Surgery for Wolff-Parkinson-White syndrome: Further experience with an epicardial approach. Circulation 1986; 74:525-529

63. Bredikis J, Bredikis A: Cryosurgical ablation of left parietal wall accessory atrioventricular connections through the coronary sinus without the use of extracorporeal circulation. J Thorac Cardiovasc Surg 1985; 90:199-205

64. Bredikis J, Bukauskas F, Zebrauskas R, et al: Cryosurgical ablation of right parietal and septal accessory atrioventricular connections without the use of extracorporeal circulation. J Thorac Cardiovasc Surg 1985; 90:206-211

65. Guiraudon GM, Klein GJ, Sharma AD, et al: Closed heart technique for Wolff-Parkinson-White syndrome: Further experience and potential limitations. Ann Thorac Surg 1986; 42:651-657

66. Guiraudon GM, Klein GJ, Sharma AD, et al: Surgical ablation of posteroseptal accessory pathways in the Wolff-Parkinson-White syndrome by a closed heart technique. J Thorac Cardiovasc Surg 1986; 92:406-413

67. Morady F, Scheinman MM, Winston SA, et al: Efficacy and safety of transcatheter ablation of posteroseptal accessory pathways. Circulation 1985; 72:170-177

68. Warin JF, Haissaguerre M, Lemetayer P, et al: Catheter ablation of accessory pathways with a direct approach. Circulation 1988; 78:800-815

69. Morady F, Scheinman MM, Kou WH, et al: Long-term results of catheter ablation of a posteroseptal accessory atrioventricular connection in 48 patients. Circulation 1989; 79:1160-1170

70. Kuck KH, Kunze KP, Geiger M, et al: Attempted ablation of left sided accessory pathways by radiofrequency current (Abstr)—Abstracts of the 38th annual scientific session of the American College of Cardiology. J Am Coll Cardiol 1989; 13:168A

71. Borggrefe M, Budde T, Podczeck A, et al: High frequency alternating current ablation of an accessory pathway in humans. J Am Coll Cardiol 1987; 10:576-582

72. Roman CA, Friday KJ, Wang X, et al: Ablation of single and multiple accessory pathways with radiofrequency current. Circulation 1989; 80 (suppl): II-323

73. Langberg JJ, Chin MC, Herre JM, et al: Catheter ablation of the atrioventricular junction using radiofrequency energy (Abstr)—Abstracts of the 38th annual scientific session of the American College of Cardiology. J Am Coll Cardiol 1989; 13:169A

74. Bardy GH, Ivey TD, Coltorti F, et al: Developments, complications and limitations of catheter-mediated electrical ablation of posterior accessory atrioventricular pathways. Am J Cardiol 1988; 61:309-316

75. Diagnostic and therapeutic technology assessment: Ablation of accessory pathways in the Wolff-Parkinson-White syndrome. JAMA 1987; 258:542-544

76. Buxton AE: Catheter ablation of atrioventricular bypass tracts—Still an investigational procedure. Circulation 1989; 79:1388-1390

77. Ryan GF, Easley RM, Zaroff LI, et al: Paradoxical use of a demand pacemaker in treatment of supraventricular tachycardia due to the Wolff-Parkinson-White syndrome. Circulation 1968; 38:1037-1043

78. Spurrell RAJ, Nathan AW, Camm AJ: Clinical experience with implantable scanning tachycardia reversion pacemakers. PACE 1984; 7:1296-1300

79. Scheinman MM: Nonpharmacologic treatment of life-threatening cardiac arrhythmias. Am Heart J 1988; 114:1291-1298

80. Mitsui T, Yamaguchi I, Koishizawa T, et al: Left thoracic sympathectomy for treatment of refractory reentrant tachycardia in concealed Wolff-Parkinson-White syndrome. Am J Cardiol 1986; 57:995-997

Medical Progress

# Perspective on Hypertension in the Elderly

BARBARA WHITCOMB, MD, *and* RICHARD L. BYYNY, MD, *Denver*

*More than half of elderly men and women have hypertension, leading to a significant risk of increased morbidity and mortality. The cause of hypertension in this age group is unknown. Left ventricular hypertrophy is frequently present, often associated with diastolic dysfunction. Systolic hypertension in the elderly increases the risk of cardiovascular disease, but there are no good data to show that the treatment of isolated systolic hypertension reduces the morbidity or mortality. Good evidence indicates that antihypertensive treatment in this group decreases cardiovascular morbidity and mortality up to age 80, so most elderly hypertensive patients should be treated. An empiric trial of nonpharmacologic therapy can be initiated in those with mild hypertension and no cardiovascular disease, but most patients will require drug therapy. Most elderly hypertensive patients have accompanying illnesses for which they may or may not be taking medications. Some antihypertensive drugs exacerbate coexisting diseases while others augment treatment regimens. Similarly, drugs may interact in a beneficial or adverse way. Finally, drug metabolism is altered by age, leading to problems with toxicity or diminished efficacy. The choice of medication should be based on all such considerations, including the cost and convenience of the drugs available.*

(Whitcomb B, Byyny RL: Perspective on hypertension in the elderly. West J Med 1990 Apr; 152:392-400)

Physicians' goals are to prevent disease when possible, to treat disease when present, and to help each patient maintain the highest quality of life possible. These hold true for all patient populations but seem to have special significance in the geriatric population where physicians strive to maintain function and independence and to prevent disability or premature mortality. In the elderly, hypertension is the single most potent, common, and remedial risk factor for cerebrovascular disease, congestive heart failure, and coronary artery disease—the major causes of cardiovascular morbidity and mortality in those older than 65.[1] Hypertension and its sequelae become more important as our geriatric population increases in number.

Although the elderly currently represent only 15% of the United States population, they consume a third of the health care dollar. The elderly population is growing two and a half times faster than the general population. The geriatric population (those older than 65) has been estimated to approach 30 million by this year.[2] Although we anticipate an evolution in the delivery and funding of health care in the years to come, the problem presents itself now: that of treating a common disorder, hypertension, in a rapidly growing population, the elderly.

## Hypertension and the Elderly

Just how common is hypertension in the elderly? The prevalence depends on the blood pressure criteria selected to define hypertension and the number of blood pressure measurements required to make the diagnosis. The risk from increasing levels of blood pressure parallels the rise in the systolic and diastolic blood pressures. The gradient of risk for each increment in blood pressure is greater with advanced age.[3] To estimate the rates or prevalence of hypertension, categories of normal, borderline, and high must be selected. Table 1 shows a simple classification scheme to categorize hypertension.[4] Because criteria to define hypertension vary, the reported prevalence of hypertension in the elderly depends on the definition. In the late 1970s, the National Health and Nutrition Survey evaluated an ambulatory population aged 65 to 74 years. The investigators chose to measure the blood pressure three times in a single visit and defined hypertension as an average pressure of greater than 140/90 mm of mercury. The overall prevalence of hypertension was 64.3%. When hypertension was defined as an average pressure of greater than 165/95 mm of mercury, the overall prevalence fell to 45.1%. As a rule, black women tended to have the highest prevalence of hypertension and white men had the lowest.[5] The 1988 report of the Joint National Committee estimated that by this year (1990), 45% of patients older than 65 would have a systolic blood pressure of greater than 160 mm of mercury or a diastolic blood pressure of more than 95 mm of mercury. If hypertension is defined as greater than 140/90 mm of mercury, the prevalence increases to 67%. In general, these figures are in agreement with several recently published articles that suggest that the prevalence of hypertension in the elderly ranges from 40% to 65%.[2,6-9]

Most clinical studies cite a 6% to 10% prevalence of isolated systolic hypertension (systolic blood pressure >160 mm of mercury with diastolic blood pressure <90 mm of mercury).[2] Kuramoto's study of 1,561 consecutive autopsies of patients aged 60 to older than 90 years revealed that 18% had isolated systolic hypertension and 37% had combined systolic and diastolic hypertension. While the percentage of patients with diastolic hypertension remained stable from

From the Division of Internal Medicine, University of Colorado Health Sciences Center, Denver.
Reprint requests to Barbara Whitcomb, MD, University of Colorado, 4200 E Ninth Ave, Box B180, Denver, CO 80262.

TABLE 1.—*Classification of Hypertension in the Elderly Based on the Level of Systolic and Diastolic Blood Pressures*

| Classification | Blood Pressure (BP), mm of mercury | |
|---|---|---|
| | Systolic | Diastolic |
| Combined hypertension | >160 | >90 |
| Borderline hypertension | 140-159 | >90 |
| Predominantly systolic hypertension | >(diastolic BP−15)2 | >90 |
| Isolated systolic hypertension | >160 | <90 |

age 60 on, the percentage of those with isolated systolic hypertension rose steadily from 7% to greater than 30% between the ages of 60 and 90.[9] Although the prevalence of isolated systolic hypertension is not as high as the prevalence of combined systolic and diastolic hypertension, it poses a major problem for elderly patients. The Framingham data indicate that the systolic blood pressure correlates better with the occurrence of ischemic heart disease, congestive heart failure, and atherothrombotic brain infarct than the diastolic blood pressure or mean arterial pressure.[10] In the European Working Party on High Blood Pressure in the Elderly trial, only the systolic blood pressure was associated with increased cardiovascular events in elderly hypertensive subjects.[11] High systolic pressures increase cardiac work, with the subsequent development of left ventricular hypertrophy and congestive heart failure. Clinicians should evaluate the baseline systolic blood pressure and attempt to reduce the systolic and the diastolic pressures in elderly persons with combined diastolic and systolic hypertension. Treatment aimed at lowering the systolic blood pressure should improve cardiac function and decrease the development of heart disease with its associated morbidity and mortality. Clinical studies to prove the efficacy of the treatment of isolated systolic hypertension are underway.

Although a rise in blood pressure with increasing age is not inevitable, persons living in industrialized nations such as the United States exhibit a rise in both diastolic and systolic blood pressures with advancing age.[12,13] Socioeconomic, cultural, and behavioral factors such as smoking, ethanol use, obesity, exercise patterns, diet, and stress may account for the time- and age-related rise in blood pressure. In the United States the systolic blood pressure rises 5 to 10 mm of mercury from ages 40 through 80. The diastolic blood pressure rises 5 to 6 mm of mercury to age 50 through 60, then levels off as a person ages.[14] Women and blacks have the sharpest rise in both systolic and diastolic blood pressures compared with whites and men, whose pressures rise the slowest. Those who have a low or normal blood pressure as young adults show the least tendency to have hypertension with age.[15]

## Risk of Hypertension in the Elderly

As stated before, cerebrovascular disease, congestive heart failure, and coronary artery disease are the major causes of morbidity and mortality in the elderly. In fact, greater than 50% of all mortality beyond age 65 is a result of cardiac or cerebrovascular disease. An estimated 40% of patients aged 65 through 74 have cardiac disease; the number rises to 50% for those older than 75. As the blood pressure increases, so does the risk of a cardiovascular event.[16] Not only are elderly persons more likely to have cardiovascular disease develop, but they are also more likely to succumb to an event. Advanced age significantly affects the survival after a stroke or myocardial infarction. A 60- to 69-year-old patient with a myocardial infarction has a 38% mortality rate, but a patient aged 80 to 89 has a 58% mortality.[17] Only 20% of patients older than 60 with stroke have a good outcome in contrast to younger stroke patients who show a favorable outcome in 30% to 50% of cases.[18] Cardiovascular mortality increases eight times in hypertensive women and two times in hypertensive men aged 65 to 74 compared with normotensive controls of the same age.[19] Several studies have shown that both combined systolic and diastolic hypertension and isolated systolic hypertension are significant risk factors for cardiovascular morbidity and mortality in the elderly.[20]

## Etiology of Hypertension in the Elderly

No one knows what causes hypertension in the elderly. The aging process itself is not entirely responsible for the development of hypertension. Remember, not all elderly persons have hypertension, but the aging process does have an effect on all major organ systems including the heart, aorta, peripheral vasculature, kidneys, and central nervous system. Changes in the body composition and chemistry with alterations in microanatomy and dynamic mechanical properties of various organ systems contribute to the complex process of aging. Some of these changes are theorized to play a part in the development of hypertension in the elderly. Hypertension in a geriatric patient is characterized by a low cardiac output and high peripheral vascular resistance.[21] The aortic wall thickness increases with age, and elasticity decreases. The aorta becomes elongated and tortuous with an increase in diameter and volume. The increase in aortic cross-sectional area results in an increase in vascular stiffness.[22] The left ventricle must pump against a stiff aorta and high peripheral vascular resistance. As a result the left ventricular end-diastolic volume increases, the stroke volume falls, and the cardiac output falls.[23] Elderly patients with hypertension are also noted to have lower intravascular volume, renal blood flow, and plasma renin levels than young hypertensive persons.[21] With increased age comes a decrease in the glomerular filtration rate and impaired sodium-conserving ability, diluting capacity, and baroreceptor sensitivity.[24,25] The baroreceptor reflexes are responsible for attenuating sudden increases or decreases in the arterial blood pressure with changes in posture.[26] Faulty autoregulation in blood pressure through alterations in baroreceptor reflex mechanisms may play some part in the development of hypertension in the elderly. It may also explain, in part, the tendency of older patients to have labile hypertension or orthostatic hypotension. The decrease in lean body weight with an increase in total body fat seen in most older patients may contribute to the development of hypertension.[27] A sedentary life-style with decreased physical activity may also play a part. It is difficult to know which of these observations are related purely to normal aging and which are related to hypertension. There have been no good age-matched studies to compare elderly normotensive and hypertensive subjects. Hypertension in the elderly remains a common disorder, extensively studied and poorly understood.

## Diagnosis of Hypertension in the Elderly

Most clinicians agree that a diagnosis of hypertension can be made only after three blood pressure measurements taken on three separate visits show pressures at or above a level

previously determined to define hypertension—usually above 140/90 mm of mercury.[28] There is some question about the accuracy of indirect (cuff) blood pressure measurements in the elderly. The young show no important difference in blood pressure whether it is measured directly (intra-arterial pressure) or indirectly. In the elderly, indirect blood pressure measurements underestimate the direct systolic blood pressure by 4 mm of mercury and overestimate the direct diastolic blood pressure by approximately 9 mm of mercury.[29] There is a consistent correlation between direct and indirect blood pressure measurements in each person. Most physicians never consider or measure the direct blood pressure. Instead, they use indirect measurements to diagnose hypertension and monitor therapy. The discrepancy between the direct and indirect blood pressure should be kept in mind when caring for elderly patients with hypertension. The blood pressure should also be measured standing and sitting to identify significant orthostatic changes.

*Errors in Diagnosis*

There are three major causes of misdiagnosing hypertension in the elderly: pseudohypertension, the auscultatory gap, and "office" or "white coat" (labile) hypertension.

One investigator suggests that as many as 15% of patients older than 65 may have pseudohypertension.[30] In the elderly sclerotic, rigid arteries may develop that compress only at high pressures. If the vessels of the arm are sclerotic, artificially high blood pressures will be obtained with a sphygmomanometer (pseudohypertension). The difference between cuff and intra-arterial blood pressures may vary from 10 to 100 mm of mercury. The Osler maneuver allows the detection of pseudohypertension.[31] To do the Osler maneuver, the clinician palpates the radial artery while inflating the blood pressure cuff. When arterial pulsations stop, the artery is assessed. If it remains rigid and palpable, the diagnosis of pseudohypertension is made. Treating patients who have pseudohypertension may be dangerous without an accurate determination of the blood pressure measured intra-arterially.

In the elderly there is often a wide gap between the first Korotkoff's sound and subsequent auscultated beats (the auscultatory gap). If the blood pressure cuff is inflated into this quiet gap, or if the first sound is not recorded, the systolic blood pressure will be underestimated. Accurate systolic pressures can be obtained by inflating the cuff to the point the palpable pulse disappears, then reinflating the cuff to this value and listening for the first Korotkoff's sound, which represents the true systolic blood pressure.

White coat or office hypertension is a transient increase in blood pressure associated with a visit to a physician's office. Patients with office hypertension usually have normal blood pressures outside the office with peaks in pressure at times of stress.

## Clinical Evaluation

A complete evaluation of an elderly patient with hypertension includes not only the blood pressure measurement but a careful history and physical examination. The patient should have the blood pressure measured in the sitting and standing positions, and an Osler's maneuver should be done. Evidence of cardiac enlargement or failure and signs or symptoms of renal failure should be sought. The history should include questions concerning smoking habits, diet and exercise habits, alcohol intake, and drug history. Although there are no screening or standard laboratory tests, many clinicians find a complete blood count, a chemistry profile with serum creatinine and cholesterol levels, a urinalysis, and an electrocardiogram useful.[16] Secondary causes of hypertension are not common in the elderly, but when a patient presents with hypertension after the age of 55, a blood pressure that is difficult to control despite appropriate three-drug therapy, resistance to an antihypertensive regimen previously effective, or accelerated hypertension, secondary sources should be considered. If the serum creatinine level rises substantially in a patient receiving an angiotensin-converting enzyme inhibitor, bilateral renal artery stenosis should be considered and an appropriate workup done. An echocardiogram or gated blood pool scan may be indicated to help guide therapy in patients with congestive heart failure, especially if the patient is to be treated with antihypertensive agents that have adverse inotropic or chronotropic effects.

## Decision to Treat

The decision to treat a patient who has hypertension involves assessing the risk-benefit ratio. In most hypertensive elderly patients, the benefits of treating hypertension outweigh the risks and side effects. Several well-done clinical trials show that antihypertensive therapy is effective in lowering the blood pressure in the elderly and that cardiovascular morbidity and mortality are reduced in patients who achieve goal blood pressures.

*Clinical Trials*

The Hypertension Detection and Follow-up Study, a community-based, randomized, controlled study, compared referred-care (private practice) to stepped-care (special care) treatment in patients with elevated diastolic blood pressures.[32] A total of 2,376 patients aged 60 through 69 were involved. The study showed that patients receiving stepped care—a combination regimen of spironolactone or chlorthalidone with reserpine or methyldopa, followed by hydralazine hydrochloride, then guanethidine monosulfate as needed to control the blood pressure—reached or surpassed their blood pressure goal (diastolic blood pressure $<90$ mm of mercury) in 60% to 75% of cases. The referred-care group—treated with an unstructured regimen by private physicians—reached their goal pressure in only 34% to 55% of cases. As a rule, the elderly patients were more likely than younger patients to reach their goal pressures. All patients showed some benefit from treatment. The stepped-care group had a lower mortality than the referred-care group and were more likely than referred-care patients to remain on active treatment for five years (79.4% compared with 54%, respectively). For those aged 60 to 69, total mortality was 16.4% lower in the stepped-care group than in the referred-care group. This was close to the 16.9% reduction in mortality for all groups. There was a 45% reduction in the incidence of fatal and nonfatal strokes but no differences in that of fatal coronary artery disease or nonfatal myocardial infarction.

The Veterans Administration Cooperative Study and the Australian Therapeutic Trial in Mild Hypertension were both studies using stepped care.[33,34] The Australian study was a single-blind, placebo-controlled, parallel trial that included 582 healthy patients aged 60 through 69 with diastolic blood pressures of 95 to 100 mm of mercury and systolic blood

pressures of more than 200 mm of mercury. The investigators first administered chlorothiazide followed by methyldopa, pindolol, or propranolol hydrochloride as needed. If the diastolic blood pressure was still elevated, clonidine hydrochloride or hydralazine hydrochloride was added. The patients on drug therapy had a mean fall in diastolic blood pressures of 13 mm of mercury compared with the patients receiving a placebo who showed a 7-mm-of-mercury drop in diastolic pressures. The trial end points were death or a specific cardiovascular event. Overall there was a 39% decrease in the number of trial end points in the elderly treated group. The improved outcome was mostly attributable to fewer cerebrovascular and nonfatal cardiovascular events.

The Veterans Administration trial was a double-blind, placebo-controlled trial in which pharmacologic treatment (hydrochlorothiazide, reserpine, and hydralazine) and nonpharmacologic treatment (salt restriction) were used to control blood pressures. The original study included 194 control patients and 186 treated patients (only men in both groups). Treated patients and control patients had initial diastolic blood pressures averaging 90 to 114 mm of mercury. Of all patients enrolled, 81 were older than 60 years. In this group of elderly patients, 62.9% of patients in the control group had morbid cardiovascular events develop compared with 28.5% in the treated group. Those with the highest blood pressure and a history of cardiovascular disease benefited the most. In each of these studies, subgroups of elderly patients were evaluated to determine the efficacy of treatment.

None of these studies, however, was designed specifically to evaluate the effect of treating hypertension in elderly patients. In contrast, the European Working Party on High Blood Pressure in the Elderly trial, as the name suggests, was designed to do that.[35] A total of 840 hypertensive men and women (blood pressures 160 to 239/90 to 119 mm of mercury) older than 60 were enrolled. A third of the patients had cardiovascular complications on entry. In a double-blind, random manner, patients received a placebo or drug (hydrochlorothiazide and triamterene). The dosage of the "diuretic" pill (placebo or drug) could be increased to two capsules per day, and methyldopa (placebo or drug) could be added to control the blood pressure as deemed necessary. After five years of treatment, blood pressures in the actively treated group fell from $183 \pm 17/101 \pm 7$ to $105 \pm 20/85 \pm 9$ mm of mercury (mean $\pm$ standard error of the mean). In the placebo group, pressures fell less impressively from $182 \pm 16/101 \pm 7$ mm of mercury to $171 \pm 25/95 \pm 9$ mm of mercury. Overall, active drug treatment reduced the cardiac mortality by 38% and cardiovascular mortality by 27%. The number of other nonfatal cardiovascular events was decreased 60% in patients receiving active treatment, mostly because of a 63% decrease in the incidence of severe congestive heart failure. There was a 52% reduction in the number of cerebrovascular events (but not mortality) in actively treated patients. These patients also showed a 90% decrease in the number having severe hypertension develop. Although there was no decrease in the number of myocardial infarctions, there were fewer fatal infarctions and a decrease in the incidence of sudden death in patients on drug treatment. A beneficial effect of active treatment was seen in men and women at all levels of systolic blood pressures, in smokers and nonsmokers, and in those with and without cardiovascular complications at the time of enrollment. There were data to suggest that even those with the mildest hypertension benefit from treatment, but the numbers were not statistically significant. In the actively treated group, there was a mild increase in fasting blood glucose and serum creatinine levels and a mild decrease in serum potassium levels. Patients receiving placebo showed a slight decrease in fasting blood glucose levels and a smaller rise in serum creatinine levels. All of the changes were clinically modest and only some were statistically significant.

After reviewing these studies, it seems reasonable to conclude that, for most patients aged 60 to 79 with mild or moderate hypertension (blood pressure >160/90 mm of mercury), the benefits of treating their hypertension outweigh the risks and side effects. In those 80 years or older, treatment decisions must be tailored to each person.[35] If the patient is a "young 80" or if disease or risk factors exist that can be exacerbated by hypertension, then treatment is usually indicated. Patients with borderline hypertension (140 to 160/90 to 95 mm of mercury) should be similarly evaluated and treated appropriately.

## Treatment Recommendations

### *Nonpharmacologic Therapy*

When the decision to treat has been made, the issue of appropriate therapy arises. In young patients with mild hypertension, nonpharmacologic intervention is sometime sufficient to lower the blood pressure into the normal range. Similar therapy has not been studied in elderly patients with mild hypertension, but it seems logical to try before prescribing drugs. An elderly patient can be asked to lose weight, exercise regularly, and restrict sodium and alcohol intake without much, if any, risk to his or her health.[36]

Weight loss has historically been the most effective nonpharmacologic intervention used in young patients. Older patients typically have a higher proportion of total body fat and a lower lean body mass than younger counterparts. If an elderly patient is more than 130% of his or her ideal weight, a trial of weight loss may help lower the blood pressure.

Exercise conditioning of the elderly is possible, and, unless there are reasons not to recommend exercise, such activity should be encouraged.

Although several small studies indicate that a fair number of elderly persons with hypertension respond to low-sodium diets, restricting dietary sodium may or may not lower the blood pressure.

Restricting alcohol intake is indicated in hypertensive patients who consume more than 4 oz of alcohol per day. Not only will their general health improve, they will, in most instances, show a drop in blood pressure.

Oral calcium supplementation has been shown to be of some benefit in lowering the blood pressure. If a patient is taking calcium supplements for other reasons—that is, to prevent osteopenia—or if there is a good antihypertensive response to a trial of calcium, then supplementation should be continued. Many women are already taking calcium supplements; prescribing calcium for normocalcemic or hypocalcemic men is a low-risk intervention.

### *Pharmacologic Therapy*

If nonpharmacologic treatment fails or a patient is ineligible for such treatment because of the blood pressure level, drug therapy is called for. The first drug chosen to treat young and middle-aged persons with hypertension has traditionally been hydrochlorothiazide. In elderly patients it is

important to consider the choice carefully and whether the drug of choice will treat other coexisting conditions or possibly exacerbate them. Other medical conditions, drug metabolism, and renal and hepatic function will usually dictate the drug choice. An effort should be made to tailor the treatment to each patient. By choosing simple drug regimens that can treat as many conditions as possible with the fewest number of medications, clinicians can increase compliance, help reduce adverse side effects, and minimize patients' confusion. In elderly hypertensive patients it is important to start with low drug doses and increase the dose slowly. The goal of therapy should be a blood pressure of less than 160/90 mm of mercury. Again the pressure should be lowered slowly to avoid sudden drops in blood pressure that can result in cerebral, coronary, and renal hypoperfusion.[36]

*Diuretics*

Based on the results of the European Working Party on High Blood Pressure in the Elderly trial, and in the absence of factors to recommend other drugs, therapy should be initiated with small doses of thiazide diuretics. In fact, the 1988 report of the Joint National Committee suggests that the elderly do well when treated with diuretics.[6] If there are no contraindications, a potassium-sparing diuretic may be used in combination with the thiazide to help control the blood pressure and maintain normal potassium levels. If renal failure is present, furosemide is a better choice. Dietary sodium restriction is recommended with diuretic treatment to minimize potassium losses and to enhance the antihypertensive effect. The average response rate in the elderly with this regimen is 60% to 70% whereas the average drop in blood pressure is 25/10 mm of mercury. Diuretic therapy is relatively cheap, easy to take, associated with few side effects, and effective in lowering the cardiovascular morbidity and mortality in the elderly. Therapy should be monitored closely to avoid dehydration, hypokalemia, and orthostatic hypotension.

*$\beta$-Blockers*

$\beta$-Blockers, although not as effective as other antihypertensive agents in controlling the blood pressure in geriatric patients, can be used effectively.[6,37] $\beta$-Blocker monotherapy is associated with a 20% response rate in patients 60 years of age.[33,38] Low-dose diuretic therapy may enhance the efficacy of $\beta$-blockers and minimize the fluid retention often associated with their use. $\beta$-Blockers are a poor choice in patients with reversible obstructive airways disease, diabetes mellitus with evidence of neuropathy, congestive heart failure, atrioventricular conduction abnormalities, bradyarrhythmias, depression, and allergic rhinitis. Conversely, patients with tachyarrhythmias, senile tremor, migraine headache, and a previous myocardial infarction may benefit doubly from using $\beta$-blockers. The metabolism of both the water-soluble $\beta$-blockers (nadolol and atenolol) and fat-soluble $\beta$-blockers (metoprolol tartrate and propranolol) may be altered in the elderly, resulting in higher plasma concentrations for a given dose of drug. Low doses are, therefore, recommended, with slow advancement as necessary. Fatigue and exercise intolerance may limit the use of $\beta$-blockers in the elderly.

*Central $\alpha_2$-Agonists*

Central $\alpha_2$-agonists (clonidine, methyldopa, guanabenz acetate, and guanfacine) are effective antihypertensive drugs and well tolerated in the geriatric population when used alone or in combination with a diuretic.[39] Adverse side effects include constipation, dry mouth, and sedation. The sedating effect of these drugs can be used to an advantage in patients who have difficulty falling asleep. Clonidine when used at bedtime can enhance sleep induction, minimizing daytime somnolence. In fact, because of the decrease in the glomerular filtration rate often seen in the elderly, the sustained effects from a single bedtime dose of clonidine make once-a-day dosing possible for some. If the drug is used twice a day, the evening dose should be greater than the morning dose. A relatively new product, transdermal clonidine, offers easy, effective blood pressure control with fewer side effects.[40] The patch, applied once a week, is usually well tolerated. Some patients may have a local reaction and are forced to discontinue the drug. The other central $\alpha_2$-agonists, methyldopa, guanabenz, and guanfacine, are equally effective but not used as commonly as clonidine.

*$\alpha_1$-Receptor Antagonists*

The $\alpha_1$-antagonists, prazosin hydrochloride and terazosin hydrochloride, are effective antihypertensive agents in the general population.[41] Their use in the elderly has yet to be studied extensively. As a rule, the $\alpha_1$-antagonists are associated with few side effects. The major side effect noted is hypotension, which is most likely to develop in those patients who are volume depleted and taking diuretics or other antihypertensive drugs. First-dose hypotension is a common phenomenon in all age groups. To avoid the adverse effects of this drop in blood pressure, patients should be instructed to take the first dose at bedtime and to remain in bed until morning. Similar precautions should be used when increasing the dose or restarting the drug after periods of withdrawal (usually initiated by the patient). The use of $\alpha_1$-antagonists may increase urine flow in elderly men with symptoms of obstructive uropathy owing to an effect on the sphincter tone.[42]

*Combination $\alpha$- and $\beta$-Blockers*

Labetalol hydrochloride, an $\alpha$- and $\beta$-adrenergic blocker, is also an effective antihypertensive agent in the elderly.[43] As with the $\alpha_1$-antagonists, the initial dose of labetalol should be small and given at bedtime. Orthostatic hypotension is the major adverse effect of $\alpha\beta$-blockers; therefore, the drugs must be used cautiously. Other side effects include nightmares, gastrointestinal disturbances, fatigue, and malaise.

*Direct Vasodilators*

Some clinicians choose to treat their elderly hypertensive patients with peripheral vasodilators such as minoxidil and hydralazine. Their use has not been tested extensively in the elderly, but they are effective in lowering blood pressures in younger subjects. The tachycardia and fluid retention associated with using vasodilators may limit their use in the elderly. Diuretics and $\beta$-blockers can help offset these effects in patients treated with multiple drugs.

*Angiotensin-Converting Enzyme Inhibitors*

The angiotensin-converting enzyme (ACE) inhibitors captopril, enalapril maleate, and lisinopril act as vasodilators. They decrease the total peripheral resistance and blood pressure without causing reflex tachycardia. Clinical studies show efficacy in the elderly without significant metabolic

effects of central nervous system side effects.[44] Angiotensin-converting enzyme inhibitors are a good choice in patients with hypertension and congestive heart failure as they have the added benefit of working to decrease the afterload and symptoms of failure. Because these drugs can cause hyperkalemia, they should be used cautiously in patients with renal failure or who are taking nonsteroidal anti-inflammatory drugs. The use of ACE inhibitors should probably be avoided completely in patients taking potassium-sparing diuretics or potassium salts. The serum creatinine level should be monitored because ACE inhibitors can impair renal function.

### *Calcium Channel Blockers*

Another class of drug that offers effective blood pressure control and relatively few side effects in the elderly is the calcium channel blocker.[45,46] Available calcium channel blockers include verapamil hydrochloride, diltiazem, nifedipine, isradapine, nicardipine hydrochloride, and nitrendipine. Nitrendipine, isradapine, verapamil sustained-release, and diltiazem sustained-release are long-acting drugs that can be taken once or twice a day. The initial dose, as with other antihypertensive medications, should be low. The calcium channel blockers may decrease the mean arterial pressure as much as 25%, a potential problem for patients with compromised cerebral, coronary artery, or renal blood flow. Verapamil and diltiazem have a depressant effect on the sinus node and atrioventricular conduction. In patients with tachyarrhythmias, this is an advantage. All calcium channel blockers are cardiac depressants, although the degree of myocardial depression varies from drug to drug. Of nifedipine, diltiazem, and verapamil, nifedipine is the weakest cardiac depressant and verapamil is the strongest. Other major side effects include headache, gastrointestinal upset, tachycardia, dizziness, edema (without fluid retention), and constipation (seen most often with the use of verapamil).

All of the drugs discussed in this article are more effective when combined with small doses of a diuretic. If the simplest regimen is sought and a patient responds to therapy with one drug, then diuretics can be omitted. The point to be made is that all drugs must be administered carefully in elderly patients who frequently have altered metabolism and different responses to drugs than young patients. Table 2 outlines the dosages, cost, adverse side effects, special considerations, and drug interactions of the commonly available antihypertensive drugs.

### *Cost of Drugs*

The cost of treatment is an important consideration in antihypertensive therapy in the elderly.[47] The total cost includes not only the purchase price of drugs, but also office visits to monitor the effect of treatment or to evaluate side effects and laboratory tests, such as serum potassium, glucose, and lipid level. If a drug is prescribed at an optimal dose that is proved effective at the first follow-up visit and requires no laboratory testing, the overall cost to the patient may be reasonable even if the drug chosen is not the least expensive.

TABLE 2.—*Estimated Cost of a Year's Supply of Antihypertensive Drugs at University Hospital Pharmacy, University of Colorado Health Sciences Center (Wholesale Price), November 1988**

| Drug | | | | | |
|---|---|---|---|---|---|
| *Generic* | *Trade Name (Manufacturer)†* | *Tablet Size, mg* | *Daily Dose/d* | *Annual Cost, $* | *Cost Per Pill, $‡* |
| Hydrochlorothiazide (HCTZ) | Esidrix (Ciba-Geigy) | *25*, 50 | 25 mg | 4§ | 0.01 |
| Chlorthalidone | Hygroton (USV Pharmaceutical) | *50*, 100 | 25 mg | 7§ | 0.02 |
| Furosemide | Lasix (Hoechst-Roussel) | *40*, 80 | 40 mg, 2× | 7§ | 0.01 |
| Spironolactone | Aldactone (Searle) | *25*, 50, 100 | 25 mg, 4× | 28§ | 0.02 |
| Triamterene | Dyrenium (Smith Kline & French) | *50*, 100 | 50 mg, 2× | 137 | 0.19 |
| Triamterene/HCTZ | Dyazide (Smith Kline & French) | *25/50* capsule | 1 capsule | 43§ | 0.15 |
| | Maxzide (Lederle) | *50/75* tablet | ½ tablet | 27 | 0.12 |
| Amiloride HCl | Midamor (Merck) | *5*, 10 | 5 mg | 47 | 0.13 |
| Reserpine | Serpasil (Ciba-Geigy) | *0.1*, 0.2 | 0.2 mg | 7§ | 0.02 |
| Methyldopa | Aldomet (Merck) | *500* | 500 mg, 2× | 79 | 0.11 |
| Clonidine HCl | Catapres (Boehringer Ingelheim) | 0.1, *0.2* | 0.2 mg, 3× | 22§ | 0.02 |
| Propranolol HCl | Inderal (Ayerst) | 40, *80* | 80 mg, 2× | 14§ | 0.02 |
| Metoprolol tartrate | Lopressor (Ciba-Geigy) | 50, *100* | 50 mg, 2× | 140 | 0.39 |
| Atenolol | Tenormin (Stuart) | 50, *100* | 50 mg | 112 | 0.62 |
| Labetalol HCL | Normadyne (Schering) | *200*, 300 | 200 mg, 3× | 262 | 0.24 |
| Prazosin HCl | Minipress (Pfizer) | 1, *2*, 5 | 2 mg, 3× | 280 | 0.26 |
| Hydralazine HCl | Apresoline HCl (Ciba-Geigy) | 10, 25, *50* | 100, 2× | 14§ | 0.01 |
| Minoxidil | Loniten (Upjohn) | 2, *5*, 10 | 5 mg, 2× | 158 | 0.22 |
| Captopril | Capoten (Squibb) | *25*, 50, 150 | 25 mg, 3× | 302 | 0.28 |
| Enalapril maleate | Vasotec (Merck) | 5, 10, *20* | 10 mg, 2× | 245 | 0.68 |
| Lisinopril | Prinivil (Merck) | 5, 10, *20* | 20 mg | 180 | 0.50 |
| Nifedipine | Procardia (Pfizer) | *10*, 20 | 10 mg, 3× | 280 | 0.26 |
| Diltiazem HCl | Cardizem (Marion) | *30*, 60 | 30 mg, 3× | 237 | 0.22 |
| Verapamil HCl | Calan SR (Searle) | *240* | 240 mg | 190 | 0.53 |
| | Calan | 40, 80, *120* | 120 mg, 2× | 51§ | 0.07 |

HCl=hydrochloride, SR=sustained release

*Retail cost to patients may be estimated at 40% to more than 100% markup above wholesale price. The retail costs to patients at an independent pharmacy are comparable to or less than at the University Hospital Pharmacy.

†Many of these drugs are made by more than one manufacturer. The selection of one manufacturer's product over another should not be construed as an endorsement of that product by either the authors or the editors of THE WESTERN JOURNAL OF MEDICINE.

‡The price per pill is based on the italicized pill size.

§Generic cost.

If the costs are high, an elderly patient may stop taking the medication or may take inadequate doses in an attempt to continue treatment. Table 2 illustrates the cost per pill and the annual cost of antihypertensive therapy for some commonly prescribed drugs. These figures were obtained from the University Hospital Pharmacy in Denver. Note that the prices listed are wholesale prices; the retail cost to the patient is much higher (40% to 100% markup). The cost is estimated to be similar nationwide.[48]

The three least expensive drugs are thiazide diuretics, reserpine, and hydralazine. Diuretics are effective in 60% to 70% of elderly hypertensive patients when used alone. The cost increases substantially if potassium salts or potassium-sparing diuretics are used or if laboratory monitoring is fre-

TABLE 3.—*Side Effects and Drug Interactions of Antihypertensive Medications*

| *Drug Category* | *Generic Drug* | *Usual Dosage Range, mg/d* | *Adverse Side Effects* | *Special Considerations* | *Drug Interactions* |
|---|---|---|---|---|---|
| Thiazide diuretics | Hydrochlorothiazide | 12.5-200 | Hypokalemia; glucose intolerance; elevated levels of uric acid, cholesterol, triglycerides; sexual dysfunction; weakness; dehydration | May be ineffective in renal failure; low potassium level can cause digoxin toxicity | Can increase lithium levels; NSAIDs can antagonize the antihypertensive effect; ACE inhibitors blunt hypokalemia |
| | Chlorthalidone | 25-100 | | | |
| Loop diuretics | Furosemide | 40-160 | Same as thiazides plus ototoxicity and tinnitus | Effective in renal failure | Can potentiate the ototoxicity of aminoglycosides |
| Potassium-sparing agents | Spironolactone | 50-100 | Hyperkalemia; spironolactone use causes gynecomastia and mastodynia; triamterene use is associated with renal calculi | Spironolactone use interferes with digoxin immunoassay | ACE inhibitors and NSAIDs can potentiate hyperkalemia and precipitate renal failure; ↑ lithium levels |
| | Amiloride | 5-20 | | | |
| | Triamterene | 100-300 | | | |
| β-Adrenergic blockers | Propranolol HCl | 80-320 | May mask signs of thyrotoxicosis and hypoglycemia; may cause bronchospasm, fatigue, insomnia, sexual dysfunction, CHF, ↑ triglycerides, ↓ high-density-lipoprotein levels | Do not use in patients with asthma, CHF, heart block (more than first-degree), sick sinus syndrome; caution in patients with diabetes mellitus or COPD; need to be tapered to discontinue | Cimetidine use may ↓ bioavailability; hydralazine use may cause ↑ drug level (inhibits hepatic metabolism); β-blockers and reserpine drop blood pressure dramatically |
| | Metoprolol tartrate | 100-450 | | | |
| | Atenolol | 50-100 | | | |
| Centrally active blockers | Clonidine HCl | 0.2, 0.6 | Drowsiness, sedation, dry mouth, fatigue, sexual dysfunction, skin rash with patch | Rebound hypertension can occur with rapid withdrawal | Tricyclic antidepressants can ↓ effects of clonidine |
| | Clonidine TTS | 1 patch/wk | | | |
| Peripherally acting blockers | Methyldopa | 500-2000 | | Methyldopa may cause liver damage and Coombs'-positive hemolytic anemia;interferes with urine measurement of catecholamines;orthostatic hypotension | |
| | Prazosin | 2-20 | 1st-dose syncope, orthostatic hypotension, weakness, palpitations | | |
| Vasodilators | Hydralazine HCl | 40-300 | Vasodilatation associated with tachycardia, fluid retention; hydralazine use causes positive antinuclear antibody test; minoxidil causes hypertrichosis | May precipitate angina in patients with coronary artery disease; lupuslike syndrome with hydralazine; minoxidil use may cause or aggravate pleural or pericardial effusion; fluid retention aggravates CHF | |
| | Minoxidil | 10-40 | | | |
| ACE inhibitors | Captopril | 50-150 | Rash, cough, angioneurotic edema, hyperkalemia, dysgeusia; captopril use causes neutropenia, agranulocytosis, proteinuria | May precipitate acute renal failure in patients with bilateral renal artery stenosis | NSAIDs plus aspirin use potentiate potassium-sparing effects |
| | Enalapril maleate | 5-40 | | | |
| | Lisinopril | 10-80 | | | |
| Calcium channel blockers | Nifedipine | 30-90 | Edema, headache; nifedipine causes peripheral edema, tachycardia; all but nifedipine associated with constipation | Use calcium channel blockers carefully in patients with CHF, contraindicated in 2nd-degree and 3rd-degree heart block; diltiazem and verapamil use may cause liver failure | Quinidine use plus these drugs causes hypotension, especially in patients with IHSS; may ↑ digoxin levels; cimetidine use can ↑ nifedipine levels; ↑ prothrombin time with any of the 3 |
| | Diltiazem HCl | 90-360 | | | |
| | Verapamil HCl | 120-480 | | | |
| | Verapamil HCl sustained-release | 240-480 | | | |

ACE=angiotensin-converting enzyme, CHF=congestive heart failure, COPD=chronic obstructive pulmonary disease, IHSS=idiopathic hypertrophic subaortic stenosis, HCl=hydrochloride, NSAIDs=nonsteroidal anti-inflammatory drugs, ↑=increased, ↓=decreased

quently done. Generic propranolol, verapamil, and clonidine are relatively inexpensive, but there are no good data on the efficacy of these generics, and dosing several times a day is required for most. The newer drugs, such as the ACE inhibitors and calcium channel blockers, will be more costly but may require less frequent laboratory monitoring or fewer visits than the older, standard drugs for side effects or altered quality of life. Once again, cost must be considered and the choice tailored to the individual patient based on clinical and economic considerations.

### *Compliance in the Elderly*

Treating the elderly can be rewarding, as most elderly patients take an active interest in their treatment and are, for the most part, compliant with therapy. Compliance varies with the number of drugs used and frequency of dosing. The best compliance—95%—is achieved with a one-drug regimen. Two-drug regimens are associated with a reported 84% compliance, while three-drug regimens are associated with 74% compliance—still good.[49] Elderly patients achieve their goal blood pressure more frequently than young patients yet do not suffer any increase in adverse drug effects. In one study, subjects aged 60 to 69 years had a lower five-year incidence of adverse reactions requiring discontinuation of a drug than did younger subjects: 29.8% and 34.38%, respectively.[50] Table 3 outlines common side effects and drug interactions associated with the various antihypertensive medications.

## Isolated Systolic Hypertension

As stated earlier, isolated systolic hypertension is a risk factor for cardiovascular morbidity and mortality in the elderly. As an established risk factor, this condition should be treated, although benefit has yet to be established in controlled clinical trials. There is no consensus among physicians about the level of blood pressure that should be treated or a maximum age that may preclude therapy.[51,52] As a general rule, patients with a mean arterial pressure—determined by

$$MAP = DBP + [(SBP - DBP)/3]$$

of greater than 110 mm of mercury can safely be treated with antihypertensive drugs. If the mean arterial pressure is less than 110 mm of mercury, treatment may be somewhat risky. The medications used to treat isolated systolic hypertension can be expected to lower the systolic blood pressure 3 to 4 mm of mercury for each 1-mm-of-mercury drop in diastolic blood pressure.[53] The level of diastolic pressure can limit the treatment of isolated systolic hypertension. Because the coronary arteries fill during diastole, care must be taken in treating isolated systolic hypertension in patients with coronary artery disease. Nonpharmacologic and pharmacologic intervention can be used successfully to treat the disorder. The same drugs used to control combined hypertension can be used for patients with isolated systolic hypertension.

## Summary

Hypertension in the elderly is a common disorder and an established risk factor for cardiovascular disease. Cardiovascular morbidity and mortality can be reduced in this population by bringing the blood pressure back to the normal range. Although a number of drug regimens are effective, an attempt should be made to individually tailor the treatment based on clinical characteristics and coexisting conditions. Therapy should be kept simple to minimize confusion and designed to maximize functional capacity and quality of life. The best outcome is obtained by a careful selection of drugs, considering age-related changes in metabolism, side effects, and other untoward effects likely to be found in the elderly. Finally, drugs should be prescribed in low doses with gradual increments in dose as needed to control blood pressure.

### REFERENCES


1. Kannel WB, Gordon T: Evaluation of cardiovascular risk in the elderly: The Framingham Study. Bull NY Acad Med 1978; 54:573-591
2. Oparil S: Introduction—Treating the older hypertensive patient—An overview. Am J Med 1988; 85(suppl 3B):1
3. Kannel WB: Some lessons in cardiovascular epidemiology from Framingham. Am J Cardiol 1976; 37:269-274
4. Working Group on Hypertension in the Elderly: Statement on hypertension in the elderly. JAMA 1986; 256:70-74
5. Hypertension prevalence and the status of awareness, treatment, and control in the United States: Final report of the Subcommittee on Definition and Prevalence of the 1984 Joint National Committee. Hypertension 1985; 7:457-468
6. The 1988 Report of the Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure. Arch Intern Med 1988; 148:1023-1038
7. Frohlich ED: Hypertension in the elderly. Curr Probl Cardiol 1988; 13:313-367
8. Smith WM: Epidemiology of hypertension in older patients. Am J Med 1988; 85(suppl 3B):2-6
9. Kuramoto K, Matsushito S, Kuwajimi I: The pathogenetic role of elderly hypertension. Jpn Circ J 1981; 45:833-843
10. Levison SP: Treating hypertension in the elderly. Clin Geriatr Med 1988; 4:1-12
11. Amery A, Birkenhäger W, Brixko R, et al: Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet 1985; 1:1349-1354
12. Abrams WB: Pathophysiology of hypertension in older patients. Am J Med 1988; 85(suppl 3B):7-13
13. Lowenstein FW: Blood pressure in relation to age and sex in the tropics and subtropics: A review of the literature and an investigation in two tribes of Brazil Indians. Lancet 1961; 1:389-392
14. Miller HW: Plan and operation of the National Health and Nutrition Examination Survey—United States, 1971-1973. Vital Health Stat [series 10a and 10b] 1973; 1:1-46
15. Szklo M: Epidemiologic patterns of blood pressure in children. Epidemiol Rev 1979; 1:143-169
16. Report of the Joint National Commitee on Detection, Evaluation and Treatment of High Blood Pressure. Arch Intern Med 1984; 144:1045-1047
17. Caird FI, Kennedy RD: Epidemiology of heart disease in old age, *In* Caird FI, Dall JLC, Kennedy RD (Eds): Cardiology in Old Age. New York, Plenum, 1976, pp 1-10
18. Ostfeld AM, Shekelle RB, Klawans H, et al: Epidemiology of stroke in an elderly welfare population. Am J Public Health 1974; 64:450-462
19. Ostfeld AM: Elderly hypertensive patient—Epidemiologic review. NY State J Med 1978; 78:1125-1129
20. Kannel WB, Sorlie P: Hypertension, *In* Paul O (Ed): Epidemiology and Control of Hypertension. Miami, Symposia Specialists, 1975, pp 553-590
21. Messerli FH, Sundgaard-Riise K, Ventura HO, et al: Essential hypertension in the elderly: Haemodynamics, intravascular volume, plasma renin activity, and circulating catecholamine levels. Lancet 1983; 2:983-986
22. Yin FCP: The aging vasculature and its effects on the heart, *In* Weisfeldt ML (Ed): The Aging Heart. New York, Raven Press, 1980, pp 137-213
23. Granath A, Jonsson B, Strandell T: Circulation in healthy old men studied by right heart catheterization of rest and during exercise in supine and sitting position. Acta Med Scand 1964; 176:425-446
24. Davies DF, Shock NW: Age changes in glomerular filtration rate, effective renal plasma flow and tubular excretory capacity in adult males. J Clin Invest 1950; 29:496-507
25. Rowe JW, Andres R, Tobin JD, et al: The effect of age on creatinine clearance in men: A cross sectional and longitudinal study. J Gerontol 1976; 31:155-163
26. Shimada K, Kitazumi T, Sadakane N, et al: Age-related changes of baroreflex function, plasma norepinephrine, and blood pressure. Hypertension 1985; 7:113-117
27. Durnin JV, Womersley J: Body fat assessed from total body density and its estimation from skinfold thickness: Measurements on 481 men and women aged from 16 to 72 years. Br J Nutr 1974; 32:77-97
28. Hypertension in the over 60's (Editorial). Lancet 1980; 1:1369
29. O'Callaghan WG, Fitzgerald DJ, O'Malley K, et al: Accuracy of indirect blood pressure measurement in the elderly. Br Med J (Clin Res) 1983; 286:1545-1546
30. Prochazka AV, Martel R: Osler's maneuver in outpatient veterans. J Clin Hypertens 1987; 3:554-558
31. Messerli FH, Ventura HO, Amodeo C: Osler's maneuver and pseudohypertension. N Engl J Med 1985; 312:1548-1551
32. Curb JD, Borhani NO, Schnaper H, et al: Detection and treatment of hypertension in older individuals. Am J Epidemiol 1985; 121:371-376

33. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension—III. Influence of age, diastolic pressure, and prior cardiovascular disease: Further analysis of side effects. Circulation 1972; 45:991-1004

34. Management Committee: Treatment of hypertension in the elderly. Med J Aust 1981; 2:398-402

35. Amery A, Birkenhäger W, Brixko R, et al: Efficacy of antihypertensive drug treatment according to age, sex, blood pressure, and previous cardiovascular disease in patients over the age of 60. Lancet 1986; 2:589-592

36. Wenger NK, Marcus FI, O'Rourke RA: Cardiovascular disease in the elderly. J Am Coll Cardiol 1987; 10:80a-87a

37. Gonzales DG, Yenkata SR: Geriatric hypertension: Antihypertensive therapy in coronary artery disease. Geriatrics 1987; 42:45-50

38. Buhler FR, Burkart F, Lutold BE, et al: Antihypertensive beta blocking action as related to renin and age: A pharmacologic tool to identify pathogenetic mechanisms in essential hypertension. Am J Cardiol 1975; 36:653-669

39. Thananopavarn C, Golub MS, Sambhi MP: Clonidine in the elderly hypertensive: Monotherapy and therapy with a diuretic. Chest 1983; 83:410-411

40. Jeunemaitre X, Ged E, Ducrocq MB, et al: Effects of transdermal clonidine in young and elderly patients with mild hypertension: Evaluation by three noninvasive methods of blood pressure measurement. J Cardiovasc Pharmacol 1987; 10:162-167

41. McNeil JJ, Drummer OH, Conway EL, et al: Effect of age on pharmacokinetics of and blood pressure responses to prazosin and terazosin. J Cardiovasc Pharmacol 1987; 10:168-175

42. Ramsay JWA, Scott GI, Whitfield HN: A double-blind controlled trial of a new $\alpha_1$-blocking drug in the treatment of bladder outflow obstruction. Br J Urol 1985; 57:657-659

43. Eisalo A, Virta P: Treatment of hypertension in the elderly with labetalol. Acta Med Scand (Suppl) 1984; 665S:129-133

44. Jenkins AC, Knill JR, Dreslinski GR: Captopril in the treatment of the elderly hypertensive patient. Arch Intern Med 1985; 145:2029-2031

45. Erne P, Bolli P, Bertel O, et al: Factors influencing the hypotensive effects of calcium antagonists. Hypertension 1983; 5(Suppl II):II97-II102

46. Muller FB, Bolli P, Erne P, et al: Use of calcium antagonists as monotherapy in the management of hypertension. Am J Med 1984; 77(Suppl 2B):11-15

47. Shulman NB, Martinez B, Buogan D, et al: Financial cost as an obstacle to hypertension therapy. Am J Public Health 1986; 76:1105-1108

48. Wright JT: Geriatric hypertension therapy: A guide to cost-effectiveness. Geriatrics 1988; 43:55-60

49. Morgan TO, Nowson C, Murphy J, et al: Compliance and the elderly hypertensive. Drugs 1986; 31(Suppl):174-183

50. Five-year findings of the Hypertension Detection and Follow-up Program—Mortality by race, sex, and age. JAMA 1979; 141:2572-2577

51. Perry HM, McDonald RH, Hulley SB, et al: Systolic hypertension in the elderly program, pilot study: Morbidity and mortality experience. J Hypertens 1986; 4(Suppl):521-523

52. Saltzberg S, Stroh J, Frishman W: Isolated systolic hypertension in the elderly: Pathophysiology and treatment. Med Clin North Am 1988; 72:523-545

53. Breckenridge MB, Kostis JB: Isolated systolic hypotension in the elderly: Results of a statewide survey of clinical practice in New Jersey. Am J Med 1989; 86:370-375

# Medical Staff Conference

## Immunotherapy for Infectious Diseases

*Discussant*
JAMES E. PENNINGTON, MD

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.*

FLOYD C. RECTOR, MD*: *Several recent developments have stimulated a resurgence of interest in the concept that serious infections may be treated or prevented using immunotherapeutics. Drawing on his extensive background in this field, James Pennington will discuss at this conference such developments as rendering human plasma-derived immunoglobulin G safe for intravenous infusion; the development of hyperimmune immunoglobulin preparations against target pathogens; monoclonal antibodies with broad-spectrum anti-gram-negative bacterial activity; and antibodies that neutralize mediators of sepsis, such as tumor necrosis factor.*

JAMES E. PENNINGTON, MD†: Immunotherapy for infectious diseases no longer simply refers to serum therapy or immunoglobulin therapy and prophylaxis (Table 1). The concept of immunotherapeutics applied to infectious disease spans immunoglobulins, hyperimmune globulins, monoclonal antibodies, and antimediators. With the expansion in our knowledge of the immune system and mediators of inflammation and sepsis, the ability to neutralize these mediators is growing as a therapeutic concept. In addition, there is an emerging potential role for cytokines such as growth factors, various interferons, and interleukins in the treatment or prevention of infection. For example, recombinant granulocyte colony-stimulating factor is currently being investigated to support the bone marrow during cancer chemotherapy. If granulocyte proliferation and function can be stimulated with this cytokine, perhaps some of the intercurrent opportunistic infections that occur during cancer chemotherapy and marrow suppression could be prevented. Also, interferons are now being used to treat leprosy and chronic viral hepatitis on an investigational basis.

### Historical Observations With Lessons for the Present

Maxwell Finland, of Harvard Medical School and Boston City Hospital, was one of the founders of antimicrobial chemotherapy in this country. Finland's early work, however, involved studies of immunotherapy for infection. In fact, he was one of the most careful clinical investigators of the concept that antibodies may be useful in the treatment of infectious disease. In one of the major papers in the early preantibiotic era, Finland described a ten-year experience at the Boston City Hospital in which hyperimmune horse serum against type I, II, III, or IV pneumococcus was used to treat acute pneumococcal infections.[1] In this paper, numerous interesting observations were described, but most important was that immunotherapy was successful in reducing mortality (Table 2). For those patients admitted with type I pneumococcal infection within three days or less of the onset of illness, controls suffered a 38% mortality compared with a mortality of 10% among the treated patients. For those admitted later after the illness began, no difference between the groups was observed. The efficacy of immunotherapy was thus validated, and an important lesson was learned: namely, that a specific diagnosis and early intervention are necessary for efficacy with antibodies against bacteria.

Table 3 reviews important early lessons regarding immunotherapy. Obviously, the timing of therapy is critical. Early and specific diagnosis, therefore, is necessary. Thus, today, in considering the optimal use of specific monoclonal antibodies or specific hyperimmune globulins for treating a given infection, rapid microbiologic diagnostic techniques ideally should be available. Immunotherapy does not come without a price. In Finland's original description, he documented considerable side effects from the horse serum, usually serum sickness.[1] Today, side effects from human plasma-derived immunoglobulins and monoclonal antibodies are rare but not absent. For example, non-A, non-B hepatitis has been transmitted by certain immunoglobulin preparations.[2] Also, allergic reactions may occur after infusion with monoclonal antibodies.[3] Thus, the safety of immunotherapeutics remains an important issue during clinical trials.

By the beginning of the 1940s, it was clear that the recently discovered antibiotics (penicillin, streptomycin) and other antimicrobial agents (sulfonamides) were more effective and safer than serum in the treatment of bacterial infections. It is not surprising that a revolutionary new method for separating and concentrating $\gamma$-globulin from human plasma,[4] developed by Cohen and co-workers at Harvard Medical School, was not widely appreciated for its thera-

*Professor and Chair, Department of Medicine, University of California, San Francisco (UCSF), School of Medicine.

†Clinical Professor, Department of Medicine, UCSF, and Director of Medical Research, Cutter, Biological Division of Miles Laboratories, Inc, Berkeley, California.

(Pennington JE: Immunotherapy for infectious diseases [Medical Staff Conference]. West J Med 1990 Apr; 152:401-405)

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
HIV = human immunodeficiency virus
Ig = immunoglobulin
IGIV = intravenous immune globulin
TNF = tumor necrosis factor

peutic implications. This plasma-derived γ-globulin-rich fraction was labeled immune serum globulin and is now called immune globulin. While this antibody-rich material clearly offered advantages over the older serum preparations, there were limitations to its use as well (Table 4).

As noted in the early trials of serum therapy, the effectiveness of antibody therapy was dose-dependent. Unfortunately, it was found that immune globulin was poorly tolerated if given by intravenous infusion, presumably due to an aggregation of immunoglobulin (Ig) G molecules and activation of the complement system. Immune globulin must, therefore, be given intramuscularly. These injections are generally painful, and the size of the dose is limited by the muscle mass (and pain threshold) of the recipient. In any event, rarely can more than 150 mg per kilogram of body weight of immune globulin be given in a single injection. Thus, while serum antibodies were concentrated severalfold by Cohen's fractionation procedure, the antibody dose that could be administered with immune globulin was still limited. In practice, this dose limitation for immune globulin has not precluded its usefulness for the prophylaxis of infectious diseases in immunodeficient patients, but it has clearly limited its role in the treatment of established infections.

In recent years two major technologic advances in the preparation of antibody-containing solutions have reestablished the viability of immunotherapy as a therapeutic modality in treating infections: the rendering of human γ-globulin safe for intravenous infusion and the development of monoclonal antibodies. As early as 1962, Barandun and colleagues offered suggestions for procedures to modify immune globulin preparations to prevent aggregation and thus reduce the incidence of adverse effects when given intravenously.[5] Importantly, it was recognized that harsh chemical or enzymatic treatment of IgG may damage the molecule and reduce or abolish its natural function.[5] A number of methods have now been developed for preparing γ-globulin for intravenous infusion (Table 5).[6(p234)]

The maximal dosage of intravenous immune globulin G (IGIV) is not limited by pain or, with rare exceptions, other acute adverse reactions. Rather, the dosage is limited by theoretic concerns, such as blocking the Fc receptors of phagocytic cells in patients with sepsis, and practical issues, such as its high cost. Currently it is recommended that dosages of IGIV not exceed 500 mg per kilogram per infusion in a septic patient. To maximize the amount of specific antibody delivered per dose, a number of hyperimmune IGIV preparations have recently been developed.

## Current Uses of Intravenous Immune Globulins in Infectious Diseases

### *Neonates*

A premature infant has a serum immunoglobulin concentration at the time of birth that is significantly below that of full-term infants. This hypogammaglobulinemic state may contribute to septic complications. It is proposed that prophylaxis with immunoglobulins might prevent some of these septic complications in premature infants, and several studies suggest that this may be possible.[7,8] Perhaps the most compelling study reported to date is from Italy.[8] High-risk neonates were stratified to small (weighing less than 1,500 grams) and comparatively larger (more than 1,500 grams) birth weights and then randomly assigned to control or globulin-treated groups. In the premature infants with very low birth weights, infections occurred in 31 of 40 controls and 22 of 43 immune globulin-treated patients. The incidence of septicemia was also significantly reduced in the globulin-treated group, as was that of septic deaths. For the larger premature infants, however, there was no significant difference in the rate of infections or of deaths for the globulin-treated versus control groups. Thus, it appears that the most immature neonates may benefit from prophylactic immunoglobulin therapy.

### *Chronic Lymphocytic Leukemia*

For years it has been debated as to whether patients with hypogammaglobulinemia who have chronic lymphocytic leukemia would benefit from globulin prophylaxis. In fact, a

TABLE 1.—*Immunotherapeutics With a Possible Role in Infectious Diseases*

| |
|---|
| Intravenous immune globulins |
| Hyperimmune immunoglobulins |
| Monoclonal antibodies, such as antiendotoxin |
| Antimediators, such as anti-tumor necrosis factor |
| Cytokines, such as granulocyte colony-stimulating factor, interferons |

TABLE 2.—*Percent Mortality From Type I Pneumococcal Pneumonia**

| *Patient Deaths* | *All Cases, %* | *Admitted After ≤3 Days of Illness, %* | *Admitted After ≥3 Days of Illness, %* |
|---|---|---|---|
| Control patients (n=70) | 31 | 38 | 30 |
| Treated patients (n=80) | 21 | 10 | 34 |

*Adapted from Finland.[1]

TABLE 3.—*Lessons From Early Pneumococcal Serum Therapy Trials*

| |
|---|
| Immunotherapy can reduce mortality and morbidity of infection |
| Timing of therapy is critical |
| Early and specific diagnosis is necessary |
| Side effects (sometimes serious) may occur |

TABLE 4.—*Advantages and Disadvantages of Immune Globulin*

| *Advantages* | *Disadvantages* |
|---|---|
| "Pure" globulin | No immunoglobulin M |
| Concentrated antibodies | Anaphylaxis (intravenous) |
| Easy to handle and store | |

TABLE 5.—*Methods to Render Immune Globulin Safe for Intravenous Infusion*

| | |
|---|---|
| Reduction and alkylation | Acidification (pH 4.25) |
| Enzyme treatment (pepsin) | Diethylaminoethyl column chromatography |

number of older studies in which immune globulin was used were unable to show a significant reduction of infection in patients with this disorder. More recently, however, high-dose intravenous immune globulin prophylaxis in these patients was shown to be useful.[9] In that study, patients had either profoundly low serum immunoglobulin levels with or without recurrent infections or relatively normal globulin values and recurrent infections. Patients were randomly selected to receive either IGIV or placebo, with a dose of 400 mg per kilogram every three weeks, for 17 doses. The result was a significant reduction in bacterial infections for the IGIV-prophylaxis group but no differences in the frequency of viral or fungal infections.

*Bone Marrow Transplantation*

Many studies have been published over the past ten years, the results of which have varied in their support for the use of prophylactic immunoglobulin therapy in patients having a bone marrow transplant.[10] Perhaps the most comprehensive randomized study reported to date is that of Sullivan and associates.[11] Patients were stratified according to the marrow source, the use of laminar flow units, conditioning regimens, and whether they were seronegative or seropositive for cytomegalovirus (CMV). Patients were randomly assigned to receive IGIV, 500 mg per kilogram weekly, from 7 to 90 days after transplantation or no immunoglobulin therapy. The preliminary results of this trial have recently been presented[11] and include the observation that the incidence of gram-negative septicemia and viral infections was reduced substantially in the globulin prophylaxis group. In addition, the incidence of interstitial pneumonitis was considerably reduced by the globulin prophylaxis, as was that of graft-versus-host disease for patients older than 20 years.

*Acquired Immunodeficiency Syndrome*

Although the treatment of human immunodeficiency virus (HIV)-associated thrombocytopenia with IGIV is perhaps the best documented use of immunoglobulin therapy in patients with the acquired immunodeficiency syndrome (AIDS), for the purpose of this discussion I will focus on the prevention of bacterial infections and the treatment of HIV itself. It has been long known that in addition to the well-recognized T-cell dysfunction in AIDS, there is also B-cell dysfunction. Lane and co-workers described increased spontaneous B-cell secretion of immunoglobulins in adult patients with AIDS and hypergammaglobulinemia and showed this to be a dysfunctional form of $\gamma$-globulin.[12] They also described decreased B-cell response in vitro to T-cell-independent mitogens and helper T-cell dysfunction. In pediatric patients, humoral immune problems are even more severe.[13] Table 6 provides a summary of humoral immune defects occurring in children with AIDS. In particular, because these patients have a limited memory cell reservoir, having not encountered as many neoantigens as have adults, the fact that they have a decreased primary response to T-cell-independent neoantigens is particularly serious. The results of these humoral immune defects might be predicted. In one recent study, 71 HIV-infected children were observed over a 3½-year period.[14] Their mean age was 31 months, and 27 (38%) of these patients had documented bacterial infections—125 episodes in all. Not surprisingly, mortality was higher in this group with recurrent bacterial infections than in the group without. Deaths were not generally due to the bacterial infections themselves; rather, the bacterial infections seemed to be a marker for a more severely disturbed immune system. These infectious complications often resulted in expensive hospital stays. The sites of the infections were mainly respiratory, with lung, upper respiratory tract, and ears, nose, and throat all commonly involved.

TABLE 6.—*Humoral Immune Defects in Children With the Acquired Immunodeficiency Syndrome*

| |
|---|
| Decreased primary response to T-cell-independent neoantigens |
| Reduced "memory cell" reservoir |
| Depressed amplification of antibody response on secondary challenge with antigen |
| Depressed IgM-to-IgG class switch |
| Decreased $IgG_2$ levels (total IgG content increased) |

With this devastating problem in mind, a number of investigators have advocated the use of prophylactic intravenous immune globulin in pediatric AIDS patients.[15,16] There are no prospective, randomized, controlled studies reported to date, but several crossover studies have been described.[17,18] One particularly interesting prospective study has been carried out in Scotland.[18] Eight HIV-infected children with ages from 9 to 48 months were selected to receive IGIV, 200 mg per kilogram, every three weeks. These eight patients were selected after showing either severe intractable diarrhea or recurrent bacterial infections (or both). In the one-year period before study entry, the cohort experienced 220 total hospital days, but they required only 56 hospital days during the first 12 months after study entry. Obviously, this resulted in reduced hospital costs. Also in the one-year period before study, the eight patients experienced 34 different serious infectious episodes, including 13 episodes of pneumonia. In the one-year period after starting immune globulin prophylaxis, there were only six infectious episodes, including four of pneumonia. Of note, four of these children before study entry showed HIV core antigenemia, and after study entry, all four reverted to a serum core antigen-negative state. In one patient, however, recurrent antigenemia did develop nine months after starting prophylaxis. The implications of this observation are not clear. Whether there was suppressive or neutralizing antibody in the immune globulins, or whether simply suppressing the recurrent opportunistic infections allowed the active HIV infection to go into remission is unclear.

Perhaps the most widely publicized clinical observations regarding passive immunotherapy in AIDS have been with those using human plasma from AIDS patients with high neutralizing antibody titers. These plasmas have been administered to other AIDS patients who were positive for the p24 antigen and who were subsequently rendered p24 antigen-negative. In one report, Jackson and associates used plasma from two donors.[19] Single infusions were given to six HIV-infected patients, and in four of the six, p24 antigenemia disappeared for about two months after the infusion. More recently, Karpas and colleagues used the same type of plasma donors with HIV-neutralizing antibodies.[20] In nine patients who were positive for the p24 antigen, the antigenemia disappeared after three successive monthly infusions of the plasma. Could these results be duplicated using intravenous immunoglobulin G rather than whole plasma? This is uncertain, as is the long-term significance and reproducibility of the observations.

## Hyperimmune Globulins

While commercially available IGIV preparations contain antibodies concentrated above their plasma concentration, it is possible to pool plasma for fractionation that has been selected on the basis of unusually high antibody titers against specific infectious pathogens. The net effect is to obtain IGIV preparations with specific antibody titers four to five times higher than those in the nonselected IGIV preparations. These globulins are known as hyperimmune immunoglobulins, and several are currently under clinical investigation (Table 7). The concept is that antibodies work by one mechanism, such as opsonization or viral neutralization, whereas antibiotic chemotherapy works by a different mechanism, and that adding these two different mechanisms together may lead to synergistic or additive efficacy in treating the infection. Probably the most widely studied hyperimmune globulins are those with a neutralizing capacity for cytomegalovirus. But there are other preparations being investigated, including hyperimmune globulins against *Pseudomonas aeruginosa,* group B *Streptococcus,* pneumococcus, and a few other organisms, such as respiratory syncytial virus. Cytomegalovirus globulin has been particularly useful in patients who have had a transplant. In one study, CMV globulin prophylaxis reduced the incidence of CMV disease in CMV-seronegative renal transplant recipients of organs from CMV-seropositive donors.[21] More recently, the combination of CMV globulin plus ganciclovir has reduced mortality from CMV pneumonia in patients having bone marrow transplantation.[22]

## Monoclonal Antibodies

The use of monoclonal antibodies for infectious diseases at present is generally confined to the treatment of gram-negative sepsis. In the United States, there are at least 100,000 or more cases of gram-negative bacteremia per year, and septic shock occurs in a fair proportion of these cases. Mortality of gram-negative sepsis without shock is not terribly high, about 10% or 15% in most series, but with progression to septic shock, the mortality increases fourfold. Thus, despite the use of antibiotics, vasopressors, and other supportive measures, sepsis is still a major therapeutic problem. Considering the large serotypic heterogeneity of gram-negative bacilli, how could broad-spectrum monoclonal antibody immunotherapy be developed? The observation that the inner portion ("core") of the cell wall for all gram-negative bacilli is similar in structure allows for the development of a single monoclonal antibody against the epitope that should cross-react with all gram-negative bacilli. This core target is often identified by the name of certain mutant bacteria that only form the core portion of the cell wall. The J-5 mutant of *Escherichia coli* is particularly well recognized, and several anti-J-5 monoclonal antibodies are now being evaluated in clinical trials.

An early clinical study has also motivated the development of anti-J-5 monoclonal antibodies.[23] In this study by Zeigler and co-workers, a control group of patients with gram-negative bacteremia and sepsis were treated with normal plasma, and a separate group received plasma from volunteers who had been immunized with a J-5 vaccine. Adding the J-5 plasma treatment significantly reduced mortality overall, particularly for those with hypotension. To date, the results of randomized trials of anti-J-5 monoclonal antibodies in septic patients have not been published.

TABLE 7.—*Intravenous Hyperimmune Globulin Preparations Currently Used in Clinical Trials for Infectious Diseases*

| | |
|---|---|
| *Pseudomonas aeruginosa* | Cytomegalovirus |
| Cutter Biological* | Cutter Biological* |
| Armour Pharmaceutical Company | Biotest |
| Sandoz Pharmaceuticals† | Massachusetts State Laboratory |
| Group B *Streptococcus* | J-5 Antiendotoxin |
| Sandoz Pharmaceuticals† | Sandoz Pharmaceuticals† |
| Pneumococcal/*Haemophilus influenzae* | Re Antiendotoxin |
| Hyland Therapeutics‡ | Hyland Therapeutics‡ |
| Biotest | |

*Division of Miles Laboratories, Inc.
†Division of Sandoz, Inc.
‡Division of Travenol Laboratories, Inc.

## Future Approaches

One promising new therapeutic concept is to use antibodies that neutralize mediators of the sepsis syndrome. The cytokine tumor necrosis factor (TNF) appears to be a particularly important mediator in sepsis.[24] Tumor necrosis factor is a 17,000-dalton protein, secreted by macrophages when they are stimulated by bacteria. In 1975 Carswell and colleagues found, in mice challenged with endotoxin, that a serum factor was released that caused necrosis of tumor, and they called this tumor necrosis factor.[25] It has subsequently been found that TNF (also known as cachectin) is an endotoxin-stimulated mediator of sepsis and septic shock.[26,27] In addition to endotoxin, certain complement components, as well as gram-positive bacteria, parasites, and even some viruses, including HIV, have been shown to stimulate monocytes and macrophages to secrete TNF. If injected into humans or animals, TNF causes fever, acidosis, and shock, all of the features that we associate with clinical septic shock. Furthermore, several studies show that in patients with sepsis, the prognosis correlates with TNF levels in their serum.[28-30] Of relevance are observations in which an immunoglobulin or an antiserum raised against TNF could neutralize endotoxin-induced lethal effects in mice or rabbits.[31,32] Recently, a monoclonal antibody that could be shown in vitro to neutralize TNF in a cell cytotoxicity assay was used in baboons challenged with intravenous *E coli.*[33] There were no survivors in untreated controls, but animals treated with anti-TNF monoclonal antibody survived if treatment was given two hours before challenge. Thus, in an in vivo primate model of sepsis, the protective capacity of an anti-TNF monoclonal antibody has been shown.

Where do we go from here? I think that the limitations of immunotherapy for infectious diseases are only those imposed by our creativity, imagination, and scientific expertise. In a decade from now, this review will likely be historically dated and a host of new and exciting concepts in the immunotherapy for infectious diseases will have emerged.

### REFERENCES

1. Finland M: The serum treatment of lobar pneumonia. N Engl J Med 1930; 202:1244-1247

2. Björkander J, Cunningham-Rundles C, Lundin P, et al: Intravenous immunoglobulin prophylaxis causing liver damage in 16 of 77 patients with hypogammaglobulinemia or IgG subclass deficiency. Am J Med 1988; 84:107-111

3. Cosimi AB, Colvin RB, Burton RC, et al: Use of monoclonal antibodies to T-cell subsets for immunologic monitoring and treatment to recipients of renal allografts. N Engl J Med 1981;305:308-314

4. Cohen EJ, Oncley JL, Strong LE, et al: Chemical, clinical and immunological studies on the products of human plasma fractionation—1. The characterization of protein fractions of human plasma. J Clin Invest 944; 23:417-432

5. Barandun S, Kistler P, Jeunet F: Intravenous administration of human gammaglobulin. Vox Sang 1962; 7:157-174

6. Alving BM, Finlayson JS: Table of immunoglobulin preparations, *In* Immunoglobulins: Characteristics and Uses of Intravenous Preparations, DHHS publication No. (FDA)-80-9005. U.S. Department of Health and Human Services, Food and Drug Administration, 1980

7. Haque KN, Zaidi MH, Haque SK, et al: Intravenous immunoglobulin for prevention of sepsis in preterm and low birth weight infants. Pediatr Infect Dis 1986; 5:622-625

8. Chirico G, Rondini G, Plebani A, et al: intravenous gammaglobulin therapy for prophylaxis of infection in high-risk neonates. J Pediatr 1987; 110:437-442

9. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia: Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. N Engl J Med 1988; 319:902-907

10. Bowden RA, Sayers M, Flournoy N, et al: Cytomegalovirus immune globulin and seronegative blood products to prevent primary cytomegalovirus infection after marrow transplantation. N Engl J Med 1986; 314:1006-1010

11. Sullivan KM, Kopecky J, Jocom J, et al: Antimicrobial and Immunomodulatory Effects of Intravenous Immunoglobulin (IVIG) in Bone Marrow Transplantation (BMT) (Abstr). 28th Interscience Conference on Antimicrobial Agents and Chemotherapy, Los Angeles, 1988

12. Lane HC, Masur H, Edgar LC, et al: Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. N Engl J Med 1983; 309:453-458

13. Bernstein LJ, Ochs HD, Wedgewood RJ, et al: Defective humoral immunity in pediatric acquired immune deficiency syndrome. J Pediatr 1985; 107:352-357

14. Krasinski K, Borkowsky W, Bonk S, et al: Bacterial infections in human immunodeficiency virus-infected children. Pediatr Infect Dis J 1988; 7:323-328

15. Calvelli TA, Rubinstein A: Intravenous gamma-globulin in infant acquired immunodeficiency syndrome. Pediatr Infect Dis J 1986; 5:S207-S210

16. Oleske JM, Connor EM, Bobila R, et al: The use of IVIG in children with AIDS. Vox Sang 1987; 52:172

17. Schaad UB, Gianella-Borradori A, Perret B, et al: Intravenous immune globulin in symptomatic pediatric human immunodeficiency virus infection. Eur J Pediatr 1988; 147:300-303

18. Hague RA, Yap PL, Mok JYQ, et al: Intravenous immunoglobulin in HIV infection: Evidence for the efficacy of treatment. Arch Dis Child 1989; 64:1146-1150

19. Jackson GG, Perkins JT, Rubenis M, et al: Passive immunoneutralization of human immunodeficiency virus in patients with advanced AIDS. Lancet 1988; 2:647-652

20. Karpas A, Hill F, Youle M, et al: Effects of passive immunization in patients with the acquired immunodeficiency syndrome-related complex and acquired immunodeficiency syndrome. Proc Natl Acad Sci USA 1988; 85:9234-9237

21. Snydman DR, Werner BG, Heinze-Lacey B, et al: Use of cytomegalovirus immune globulin to prevent cytomegalovirus disease in renal transplant recipients. N Engl J Med 1987; 317:1049-1054

22. Reed EC, Bowden RA, Dandliker PS, et al: Treatment of cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin patients with bone marrow transplants. Ann Intern Med 1988; 109:783-788

23. Ziegler EJ, McCutchan JA, Fierer J, et al: Treatment of gram-negative bacteremia and shock with human antiserum to a mutant *Escherichia coli*. N Engl J Med 1982; 307:1225-1230

24. Beutler B, Cerami A: Cachectin: More than a tumor necrosis factor. N Engl J Med 1987; 316:379-385

25. Carswell EA, Old LJ, Kassel RL, et al: An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci USA 1975; 72:3666-3670

26. Tracey KJ, Beutler B, Lowry SF, et al: Shock and tissue injury induced by recombinant human cachectin. Science 1986; 234:470-474

27. Bauss F, Droge W, Mannel DN: Tumor necrosis factor mediates endotoxic effects in mice. Infect Immun 1987; 55:1622-1625

28. Waage A, Halstensen A, Espevik T: Association between tumour necrosis factor in serum and fatal outcome in patients with meningococcal disease. Lancet 1987; 1:355-357

29. Girardin E, Grau GE, Dayer JM, et al: Tumor necrosis factor and interleukin-1 in the serum of children with severe infectious purpura. N Engl J Med 1988; 319:397-400

30. Debets JMH, Kampmeijer R, van der Linden MPMH, et al: Plasma tumor necrosis factor and mortality in critically ill septic patients. Crit Care Med 1989; 17:489-494

31. Beutler B, Milsark IW, Cerami AC: Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin. Science 1985; 229:869-871

32. Mathison JC, Wolfson E, Ulevitch RJ: Participation of tumor necrosis factor in the mediation of gram-negative bacterial lipopolysaccharide-induced injury in rabbits. J Clin Invest 1988; 81:1925-1937

33. Hinshaw LB, Tekamp-Olson P, Chang ACK, et al: Survival of primates in $LD_{100}$ septic shock following therapy with antibody to tumor necrosis factor (Abstr). Circ Shock 1989; 27:362

# Epitomes

## Important Advances in Clinical Medicine

# Obstetrics and Gynecology

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in obstetrics and gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in obstetrics and gynecology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on Obstetrics and Gynecology of the California Medical Association, and the summaries were prepared under its direction.*

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

## Avoiding Pregnancy in Isotretinoin Users

ACNE VULGARIS is a common dermatologic disorder among adolescents and young adults. Although universally considered to be a cosmetic nuisance, acne vulgaris can usually be controlled adequately using topical agents such as benzoyl peroxide combined with topical or parenteral antibiotics. Severe cases of cystic acne that do not respond to these measures often show a dramatic and prolonged remission to systemic therapy with isotretinoin (Accutane), a synthetic derivative of vitamin A. Among the adverse effects noted with isotretinoin, however, is a strong embryopathic effect causing spontaneous abortions, stillbirths, and congenital anomalies in the offspring of patients taking the drug.

In long-term follow-up, patients on isotretinoin therapy have abatement of their acne in 65% to 90% of cases. There are no alternatives to isotretinoin that can offer comparable remission rates. Side effects have generally been mild and easily managed and include skin and eye irritation, musculoskeletal pain, and headaches. The single most important risk associated with isotretinoin use is related to the intrauterine exposure of a developing fetus to the embryopathic effects of the drug. Of 36 patients who continued their pregnancies after receiving isotretinoin, 8 (22%) had spontaneous first-trimester abortions, 23 (64%) had normal infants, and 5 (14%) had malformed infants with characteristic craniofacial, thymic, and cardiac anomalies. Isotretinoin is not mutagenic, nor is it stored in tissues as is vitamin A, and its tissue half-life is 10 to 20 hours. For these reasons it does not appear that isotretinoin causes teratogenicity beyond the period of dosing. This conclusion is supported by clinical studies. Clearly, because many candidates for isotretinoin therapy are women of childbearing age, this high rate of fetal damage mandates preventing pregnancy in users of the drug.

Current recommendations for the use of isotretinoin include limiting its use only for patients with severe cystic acne unresponsive to conventional agents, careful patient education regarding the need for adequate contraception, and assessing a patient's reliability in following a contraceptive regimen. A sensitive pregnancy test should be negative within the two weeks before initiating therapy and pregnancy tests done monthly to confirm the effectiveness of the contraceptive method. Therapy should be initiated on the second or third day of the next normal period and adequate contraception used, preferably with two methods, during the dosing interval and for one month before and after therapy. Finally, there should be adequate informed consent and documentation. The manufacturer is currently funding gynecologic consultation for women of reproductive age using isotretinoin to ensure adequate contraception counseling and informed consent.

RON E. SWENSEN, MD
*Stanford, California*

REFERENCES

Lammer EJ, Chen DT, Hoar RM, et al: Retinoic acid embryopathy. N Engl J Med 1985; 313:837-841

Shalita AR, Armstrong RB, Leyden JJ, et al: Isotretinoin revisited. Cutis 1988; 42:1-19

## An Ovarian Cancer Tumor Marker, CA 125, Comes of Age

AN ANTIGEN COMMON to fetal coelomic epithelium and its adult derivatives, CA 125, has received intensive research and now practical clinical scrutiny in the management of ovarian carcinomas of an epithelial origin. CA 125 is tested in the serum of patients using a monoclonal antibody isolated by somatic cell hybridization techniques.

CA 125 may be found in the pleura, pericardium, peritoneum, fallopian tubes, tracheobronchial epithelium, endometrium, cervical mucus, seminal fluid, amniotic fluid, and other tissues, usually in quantities small enough to keep the serum level below 35 U per ml. More than 80% of patients with nonmucinous ovarian epithelial tumors will have elevated levels of CA 125 measurable in their serum. Whereas 59% of patients with stage I and II ovarian cancer have elevated CA 125 levels, this increases to 91% for those with stage IV disease. Studies have shown that when the preoperative level of CA 125 is less than 100 U per ml, almost all tumors can be optimally debulked. In contrast, when the preoperative CA 125 level exceeds 1,000 U per ml, even a radical operation leaves gross residual disease. Patients who are apparently disease-free following therapy and who subsequently have elevated CA 125 levels will inevitably manifest clinical disease, usually within three to five months.

Many investigators have used CA 125 levels to learn more

about the role of "second-look" laparotomy in the management of ovarian carcinoma. Here the sensitivity of the test is only 33%, but the specificity is 100%. The negative predictive value is 57%, and the positive predictive value is 100%. Thus, a second-look laparotomy is unnecessary in a patient with an elevated CA 125 level except in a research setting where the quantification of disease is essential for evaluating experimental protocols.

Several studies have investigated the usefulness of CA 125 levels as a screening test. Evaluating 1,020 female blood donors using a cutoff of 65 U per ml resulted in a 1.8% positive test rate. Of these, 0.7% were pregnant and only 0.3% tested positive at a second screening. Cervical adenocarcinoma, endometrial adenocarcinoma, fallopian tube carcinoma, and nongynecologic cancerous lesions such as those of the pancreas, lung, liver, breast, colon, stomach, and biliary tract have also been associated with elevated CA 125 levels. Yet elevated CA 125 levels do not necessarily imply the presence of malignancy, as elevations have also been seen with benign conditions such as pregnancy, endometriosis, menstruation, pelvic inflammatory disease, pancreatitis, peritonitis, benign ascites, and leiomyomata. Selecting a patient population with a pelvic mass for screening CA 125 levels increases the usefulness of the test. Here the sensitivity is 93% and the specificity is 87%.

In conclusion, CA 125 levels are useful in the management of ovarian carcinoma, as levels correlate with the volume of ovarian cancer present. CA 125 functions as a leading indicator of disease progression but loses considerable sensitivity during the course of disease. Likewise the predictive value of a positive test is excellent, but a decline in the value of a negative test is observed during therapy. The selection of drug-resistant cell lines that have lost the ability to make CA 125 undoubtedly contributes to these results. Further research in the area of tumor markers now focuses on the usefulness of the simultaneous measurement of several markers. It is hoped that such an approach will further facilitate the diagnosis and treatment of ovarian carcinoma.

RICHARD E. BULLER, MD, PhD
PHILIP J. DiSAIA, MD
*Irvine, California*

REFERENCES

Atack DB, Nisker JA, Allen HH, et al: CA 125 surveillance and second-look laparotomy in ovarian carcinoma. Am J Obstet Gynecol 1986; 154:287-289

Bast RC, Hunter V, Knapp RC: Pros and cons of gynecologic tumor markers. Cancer 1987; 60 (Suppl 8):1984-1992

Montag TW: Tumor markers in gynecologic oncology. Obstet Gynecol Surv 1990; 45:94-105

## Drug Therapy for Genital Herpes

ACYCLOVIR, a synthetic purine nucleoside analogue, is effective when taken orally or intravenously for primary or recurrent genital herpes. During a one-year treatment trial for frequently recurring genital herpes—that is, six or more recurrences per year—the likelihood of being symptom-free for a year was increased from 2% to 44% and the mean number of recurrences reduced from 11.4 to 1.8. This degree of efficacy has led to longer treatments. But concerns that remain unanswered include the probability of viral resistance developing and increased or additional toxicity. With short-term courses, the most common adverse effects are nausea and vomiting, occurring in about 3% of patients.

The intravenous use of acyclovir requires admitting to hospital and is generally reserved for patients with life-threatening infections. Topical acyclovir is not as effective as oral, has limited efficacy in treating recurrent disease, and has no demonstrated ability to prevent recurrences. For primary genital herpes, administering acyclovir orally, 200 mg five times a day for five to ten days, has been effective in reducing the duration of shedding and severity and duration of symptoms.

Acyclovir prophylaxis—400 mg twice a day—for patients with frequent or severe recurrences has been administered for at least a year in clinical trials. Most cases with acyclovir-resistant organisms have been found in immunocompromised patients. Such resistance has thus far not been associated with progressive disease, and in most instances subsequent recurrences were caused by acyclovir-sensitive organisms. Further studies are required to determine whether long-term suppression reduces or facilitates the emergence of clinically important drug-resistant mutants in this population.

The use of acyclovir in pregnancy, breast-feeding mothers, or newborns has not been shown safe. The Burroughs Wellcome Company has a registry of its use in pregnancy (telephone number [919] 248-4017). No specific adverse effects on mothers or fetuses have been recognized. For women with primary herpes in pregnancy, some authors have recommended using acyclovir because of initial reports of associated preterm labor and slowed intrauterine growth rate. Others, however, would only recommend its use during pregnancy or childhood for life-threatening disease or herpes simplex virus infection of immunocompromised patients. Women with visible genital herpes at the beginning of labor are advised to have delivery by cesarean section to avoid the serious consequences of neonatal herpes. Many cases of neonatal herpes result from genital excretion of herpes simplex virus type 2 by a mother who may never have experienced genital herpes symptoms. Viral cultures before labor do not predict later exposures, but cultures obtained during labor of women with previous genital herpes may be valuable in identifying babies at risk for infection and lead to more timely treatment.

PAUL A. HENSLEIGH, MD, PhD
*Santa Clara, California*

REFERENCES

Corey L, Spear PG: Infections with herpes simplex viruses (pts 1 and 2). N Engl J Med 1986; 314:686-691, 749-757

Gibbs RS, Amstey MS, Sweet RL, et al: Management of genital herpes infection in pregnancy (Editorial). Obstet Gynecol 1988; 71:779-780

Mertz GJ, Jones CC, Mills J, et al: Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection—A multicenter double-blind trial. JAMA 1988; 260:201-206

Nusinoff-Lehrman S, Douglas JM, Corey L, et al: Recurrent genital herpes and suppressive oral acyclovir therapy: Relationship between clinical outcome and in-vitro drug sensitivity. Ann Intern Med 1986; 104:786-790

## β-Streptococcal Cultures in Obstetrics

β-HEMOLYTIC STREPTOCOCCI play a role in two major areas of obstetrics: puerperal fever (primarily group A or *Streptococcus pyogenes*) and antepartum and intrapartum infections (primarily group B or *Streptococcus agalactiae*). All standard antibiotic regimens for the treatment of puerperal fever or postpartum endomyometritis include coverage for group A streptococci, and this organism is no longer responsible for the mortality that it was in the past. Group B streptococci, on the other hand, have recently been recognized as important pathogens in neonatal sepsis and possibly as etiologic agents for preterm premature rupture of the membranes and chorioamnionitis.

About 10% to 30% of pregnant women carry group B streptococci in the birth canal. The rate of carriage seems to be higher in white women younger than 20 years. At birth, approximately 10% to 15% of infants delivered of carrier mothers will become colonized (as opposed to infected) with the organism. The attack rate for true infection, which can result in severe sepsis and a 50% neonatal mortality rate, is about 1 in 1,000 at term but much higher in a preterm infant, women with intrapartum fever, or in premature rupture of the membranes. Thus, the question of how to prevent infection with group B streptococci is difficult to answer and has led to controversy among experts in perinatology and neonatology. If all pregnant women were to be screened and treated to eradicate the infection during pregnancy, such treatment would benefit only the 5% of patients who may experience preterm labor or premature rupture of the membranes and the 1 per 1,000 term infants who will contract group B streptococcal sepsis. This benefit would be at the cost of administering ampicillin to as many as 30% of all pregnant women. Furthermore, many such patients would become recolonized by the reservoir of organisms in the rectum; penicillinase-producing bacteria prevent the eradication of this reservoir. Repeated culturing and retreatment throughout the pregnancy would be necessary. Thus, most experts think that only patients with premature rupture of the membranes, preterm labor, or maternal fever during labor, or patients at risk for such events (twins, triplets, history of premature rupture of the membranes or preterm labor) should be cultured for group B streptococci and treated. For such patients, the best technique is to swab the outer third of the vagina, as this area provides the highest yield of cultures positive for the organism. Those patients with positive cultures and premature rupture of the membranes should be treated with ampicillin given intravenously, 1 gram every six hours, for five days or until delivery; cultures should be repeated every one to two weeks and treatment repeated if recolonization has occurred. Patients with intact membranes may be given oral ampicillin, 500 mg every six hours for five to seven days. For those patients with active labor or prematurely ruptured membranes, an alternate scheme is to treat all on admission until culture results become available. Experts appear to be equally divided concerning the relative risks and benefits of such an approach.

Certain patients should probably be screened and treated throughout the entire period of fetal viability to suppress group B streptococci colonizing the birth canal. This group includes patients with cervical cerclage, those with a previous infant who died of group B streptococcal sepsis, and patients at extremely high risk of preterm labor or premature rupture of the membranes. For this group, prescribing ampicillin, 500 mg by mouth every six hours, from approximately 24 weeks to delivery is appropriate. Penicillin V potassium, while effective against group B streptococci, has not been adequately tested and may allow an overgrowth of gram-negative organisms in the vagina.

At present, then, routine screening of all pregnant women for group B streptococci is not recommended, as most will have a term birth and only 10% to 30% will be colonized at the time of screening; colonization may occur after a negative screen as well. Treatment of sexual partners also is not of benefit, as the major source of recolonization of the birth canal is the reservoir of organisms in the rectum.

If group B streptococci are searched for and eradicated in a patient at high risk for preterm delivery, the severe neonatal consequences of this infection in newborns can be reduced.

R. HAROLD HOLBROOK, JR, MD
*Stanford, California*

REFERENCES

Boyer KM, Gotoff SP: Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. N Engl J Med 1986; 314:1665-1669

Minkoff H, Mead P: An obstetric approach to the prevention of early-onset group B β-hemolytic streptococcal sepsis. Am J Obstet Gynecol 1986; 154:973-977

## Estrogen Hormone Replacement to Minimize Cardiovascular Risk

In the United States, heart disease is the leading cause of death in women. More than half of all women will die of some sort of cardiovascular disorder. The incidence of cardiovascular disease in women is less than that in men until the menopause occurs. After menopause, the cardiovascular disease incidence increases at the same rate as in men so that by the age of 60 it approaches that of men and by the age of 90 the disease is equally present in both sexes.

As shown by the Framingham study and others, the risk for cardiovascular disease is related to a great extent to the level of blood lipids. In particular, high levels of triglycerides, low-density lipoprotein (LDL), and total cholesterol and low levels of high-density lipoprotein (HDL) place one at an increased risk for cardiovascular disease. Currently 50% of women in the United States have a total blood cholesterol level greater than that recommended by the National Institutes of Health. Because a 1% decrease in the cholesterol level produces a 2% decrease in the incidence of coronary artery disease, efforts to reduce blood cholesterol levels are warranted.

Following the menopause, levels of cholesterol and LDL increase and levels of HDL decrease. The replacement of estrogen after either the natural menopause or surgical castration has been shown to prevent these changes and favorably alter the lipid profile in women. Estrogen therapy decreases total cholesterol and LDL levels whereas it increases HDL levels. If the risk reductions associated with these changes in blood lipids are combined, a significant reduction would be expected in the risk of cardiovascular disease with postmenopausal estrogen replacement therapy. Several recent case-control and cohort studies have shown this decreased risk.

There are several estrogen preparations available on the market today. It is difficult to summarize the published data because of the various routes of administration, doses, and preparations used. Nevertheless, trends can be identified. When estrogen is given orally, it lowers cholesterol and LDL levels and raises HDL levels, but it may take up to several months for these beneficial effects to occur. When estrogen is delivered percutaneously, the favorable effects on lipids are reduced.

Because of the risk for endometrial hyperplasia and malignancy, the addition of progestin to estrogen replacement regimens is necessary in women who have a uterus. Unfortunately, the progestins have an effect on blood lipids opposite to that of estrogens and tend to raise cholesterol and LDL levels and lower HDL levels. In studies that have evaluated the combination of estrogen plus progestin, the effect on blood lipids depends to a great extent on the progestin chosen. Specifically, the 19-nortestosterone derivatives of

progesterone—norethindrone and norgestrel—tend to reverse the beneficial changes seen with estrogen alone, whereas medroxyprogesterone acetate has the least, if any, adverse effect on blood lipids.

The preponderance of data would indicate that estrogen replacement therapy after menopause elicits a cardioprotective effect. The effect of adding progestin to estrogen replacement is unknown at this time, but because progestin is necessary to reduce iatrogenic malignancy, it must be added. In choosing a progestin, the lowest dose possible should be used and a product prescribed that has the least undesirable effects on blood lipids. Thus, the most appropriate combination would include medroxyprogesterone acetate added to an orally prescribed estrogen.

L. MICHAEL KETTEL, MD
*San Diego*

REFERENCES

Bush TL, Barrett-Connor E, Cowan LD, et al: Cardiovascular mortality and noncontraceptive use of estrogen in women: Results from the Lipid Research Clinics Program Follow-up Study. Circulation 1987; 75:1102-1109

Corson SL: Impact of estrogen replacement therapy on cardiovascular risk. J Reprod Med 1989; 34:729-746

Matthews KA, Meilahn E, Kuller LH, et al: Menopause and risk factors for coronary heart disease. N Engl J Med 1989; 321:641-646

## Gonadotropin-Releasing Hormone Agonist Treatment of Endometriosis and Myomas

OVER THE PAST decade, several structural analogues of gonadotropin-releasing hormone (GnRH) have been described that simulate its action if administered in a pulsatile fashion (agonists) and counteract its effects if given in a nonpulsatile fashion (antagonists). A down regulation of pituitary GnRH receptors results in an initial release of luteinizing and follicle-stimulating hormone reserve pools in gonadotrophs, followed by a protracted state of decreased gonadotropin secretion and, therefore, decreased ovarian estradiol ($E_2$) production. Because these agents promote a hypoestrogenic state, their usefulness lies in the treatment of $E_2$-dependent disorders including uterine leiomyomata and endometriosis.

Several studies have shown that treatment with a GnRH agonist will ameliorate symptoms associated with uterine leiomyomata. The response of individual fibroids to GnRH-agonist therapy varies widely, with a 10% to 80% decrease in size reported after three to six months of treatment, presumably because of different $E_2$ sensitivities of fibroids—such as more fibrous tumors with decreased $E_2$ sensitivity. In general, a marked reduction in fibroid size occurs by three months of treatment. An overall decrease in total uterine volume, more predictable than a decrease in myoma size, is also complete by about three months of treatment. As fibroids decrease in size, tissue planes are easier to identify and surgical extirpation is easier. In addition, uterine blood flow is diminished in the hypoestrogenic state induced by the GnRH agonist. Amenorrhea preoperatively allows a patient to replenish her hemoglobin supplies and to bank autologous blood. Also, decreased blood loss at the time of the operation decreases the need for intraoperative or postoperative blood transfusions and the likelihood of postoperative adhesion formation. Gonadotropin-releasing hormone agonists are best used as adjuncts to surgical treatment because once treatment is stopped and ovarian function resumes, usually within six weeks after stopping therapy, fibroids will regrow to their pretreatment size within four months.

Endometriosis implants are exquisitely sensitive to $E_2$, and GnRH-agonist therapy with ensuing hypoestrogenism is well suited to the treatment of this condition. About 80% of women with endometriosis and pelvic pain will experience notable amelioration of their symptoms within six weeks of therapy. An objective response of pelvic endometriosis to GnRH-agonist therapy has been documented, and conservative surgical therapy is generally easier after several months of treatment because of a decreased vascularity of the lesions and easier tissue planes for dissection. As with fibroids, the effects of the GnRH agonists are at best temporary, and the benefits of treatment must be weighed with the risks associated with hypoestrogenism, including decreased (reversible) bone density and possible alterations in high- and low-density lipoprotein cholesterol.

The only GnRH agonist that has been approved by the Food and Drug Administration is leuprolide acetate (Lupron, TAP Pharmaceuticals, North Chicago), and this approval is for prostate cancer treatment. Leuprolide is available in subcutaneous or intramuscular (depot) form. Doses of 0.5 to 1.0 mg subcutaneously daily for three months for fibroids or for six months for endometriosis are generally recommended. Alternatively, 3.75 mg given intramuscularly every 28 days is recommended for the depot form of the drug. It is advisable to begin administering it between days 1 and 3 of the menstrual cycle to obtain rapid ovarian suppression. Most women will become amenorrheic by four weeks of therapy. The main side effects are hot flashes and headaches. Patients expected to be on GnRH-agonist therapy for a protracted course would benefit from bone densitometry studies. Monthly checks of cholesterol levels may be useful.

LINDA C. GIUDICE, MD, PhD
*Stanford, California*

REFERENCES

Friedman AJ, Barbieri RL: Leuprolide acetate: Applications in gynecology. Curr Probl Obstet Gynecol Fertil 1988; 11:205-236

March CM: Update: Uses of GnRH agonists in gynecologic practice. Endocr Fertil Forum 1989; 12:1-6

## Endometrial Ablation

ENDOMETRIAL ABLATION using the neodymium:YAG [yttrium-aluminum-garnet] laser resectoscope with roller-ball or wire-loop electrocautery is an effective alternative to hysterectomy for women with excessive uterine bleeding refractory to surgical or medical therapy. It is an outpatient procedure done under general or occasionally regional anesthesia with minimal inconvenience, cost, and almost no discomfort to the patient. With recent approval by the Food and Drug Administration, this procedure is no longer considered experimental. It is for women whose uterus is otherwise normal or contains small fibroids, who have unusually heavy or prolonged bleeding or excessive intermenstrual bleeding. Before the procedure is done, they should have had a hysteroscopy with endometrial biopsy or dilatation and curettage to rule out endometrial carcinoma, endometrial atypia, endometrial polyp, or submucosal myoma. The first two are contraindications to endometrial ablation, and the latter two can usually be treated specifically without the need for ablation. An adequate trial of hormonal management to control bleeding is recommended before ablation.

The basic principle of endometrial ablation is to destroy the endometrium, hence controlling excessive menstrual flow. The procedure is done by inserting a hysteroscope into the uterine cavity, distending it with a clear fluid medium to

allow good visualization, and systematically ablating the endometrium with a laser fiber or roller-ball cautery. The laser fiber is introduced through a channel in the hysteroscope. The laser beam is directed through the fiber to the endometrium to destroy it. The patients' recovery times vary from two hours to one day, with the postoperative use of aspirin or acetaminophen adequate for pain relief. Danazol or leuprolide acetate may be used for two months preoperatively to cause a pseudomenopause by suppressing the pituitary and blocking the follicle-stimulating hormone and leutinizing hormone. This makes a woman anovulatory and amenorrheic, thereby decreasing the thickness of the endometrium and allowing a more accurate and quick destruction of the uterine lining.

Over the past ten years approximately 2,500 patients were studied at several centers. Fewer than 10% of women needed the procedure repeated or a hysterectomy. Of the other patients, half of the women had minimal spotting only, while the other half had no menstrual flow at all. Considerable problems have been reported with this procedure, including bowel damage from uterine perforation, fluid overload or electrolyte imbalance from the distention medium, and bleeding during or after the procedure. The treatment of excessive menstrual flow—that has not been resolved after appropriate hormonal therapy, dilatation and curettage, or both—by endometrial ablation may be a viable alternative to hysterectomy. This may become the standard therapy in the future for appropriately selected cases. Women who have this procedure should be aware that they are likely to have a small amount of bleeding. These patients may make up 20% to 30% of hysterectomy candidates.

ARNOLD KRESCH, MD
*Stanford, California*

REFERENCES

DeCherney AH, Diamond MP, Lavy G, et al: Endometrial ablation for intractable uterine bleeding: Hysteroscopic resection. Obstet Gynecol 1987; 70:668-670

Goldrath MH, Fuller TA, Segal S: Laser photovaporization for the treatment of menorrhagia. Am J Obstet Gynecol 1981; 140:14-19

Lomano JM: Nd:YAG laser ablation of early pelvic endometriosis: A report of 61 cases. Lasers Surg Med 1987; 7:56-60

## Medical Treatment of Ectopic Pregnancy

ECTOPIC GESTATIONS account for about 1% of all pregnancies in the United States. The availability of sensitive human chorionic gonadotropin (hCG) assays and the improvement of ultrasound technology, including the recent introduction of the vaginal probe, have facilitated the early diagnosis of ectopic pregnancies before they rupture. This has enabled obstetricians to follow a conservative approach in the treatment of ectopic gestations. The goal of such treatment is to remove the products of conception with minimal damage to the involved tube. Typically, this has been achieved by surgical management that often involves a laparotomy, although the laparoscopic removal of the products of ectopic pregnancies is gaining more acceptance.

Because of these improved methods of diagnosis, the nonsurgical management of ectopic pregnancies, both expectant management and medicinal therapy, has been used with increasing frequency in the past few years. Expectant management, which has been described in the literature for 30 years, is now much safer. Patients with falling hCG titers can often be observed for the spontaneous resolution of their ectopic gestation. The probability of such resolution is greater when the serum hCG level at diagnosis is less than 1,000 IU per liter. The hCG level should be monitored until it becomes undetectable, which usually takes two to three weeks. On the other hand, expectant management may be associated with an inflammatory reaction at the site of the ectopic gestation and may not be the method of choice when future pregnancy is desired.

Drug therapy consists primarily of using methotrexate. This agent has been known for years to be effective in treating trophoblastic disease and has also been used in the management of abdominal pregnancy. Several reports have suggested that it can be used to treat selected unruptured tubal pregnancies. The course of therapy is usually eight days; 1 mg per kilogram of body weight of methotrexate is given intramuscularly on days 1, 3, 5, and 7, and 0.1 mg per kilogram of body weight of leucovorin calcium (citrovorum factor) is given intramuscularly on days 2, 4, 6, and 8 to minimize toxicity. Most patients need only one course. The mean time to resolution is about four weeks. This method is reported to be safe when the ectopic mass is smaller than 3 cm with an hCG level of less than 10,000 IU per liter. It is contraindicated when there is sonographically detectable fetal cardiac activity because of the significant risk of hemorrhage at the time of disrupting the pregnancy. If these criteria are respected, the chance of resolution is more than 90%. The toxic effects of methotrexate use, seen in 20% to 30% of patients, include stomatitis, elevation in liver function test values, and slight bone marrow suppression.

A follow-up hysterosalpingogram after nonsurgical therapy for tubal pregnancy shows tubal patency on that side in 50% to 75% of cases. While this number is encouraging, it does not prove the absence of a mechanical impairment of tubal ovum transport, and prospective studies are needed to compare the fertility of patients treated medically with that of surgically treated patients. Women with small, unruptured ectopic masses and rising hCG titers who wish to maintain fertility are probably best treated surgically, possibly through laparoscopy. Methotrexate can be used in those instances where a conservative operation would be associated with increased morbidity, such as with interstitial or cervical ectopic gestations.

AMIN A. MILKI, MD
JAMSHID MOOSSAZADEH, MD
*Stanford, California*

REFERENCES

Ory SJ, Villanueva AL, Sand PK, et al: Conservative treatment of ectopic pregnancy with methotrexate. Am J Obstet Gynecol 1986; 154:1299-1306

Sauer MV, Gorrill MJ, Rodi IA, et al: Nonsurgical management of unruptured ectopic pregnancy: An extended clinical trial. Fertil Steril 1987; 48:752-755

Vermesh ML: Conservative management of ectopic gestation. Fertil Steril 1989; 51:559-567

## New Therapies for Genital Warts

PUBLISHED RANDOMIZED clinical trials have not established the treatment of choice for genital warts; no one treatment has been shown to be consistently superior to others. Hence, the choice of treatments may be based on the site of infection, size and number of lesions, and cost. Of note, observation without treatment may be an appropriate option for some patients because about a third of all genital warts disappear spontaneously within six months.

The topical treatment of genital warts predominates. Topical fluorouracil has been found to be more useful in treating vaginal than vulvar warts. Several regimens have been effective. An additional use for fluorouracil is as adjunctive therapy to prevent recurrence after warts are ablated. Bi-

weekly application has led to a substantial decrease in the incidence of the recurrence of lesions over a six-month interval. Halogenated acetic acids (trichloroacetic or bichloroacetic acid) are probably superior to podophyllin. With these acids, there appears to be less pain and tissue reaction than with podophyllin, and systemic toxicity is not a concern. Lesions are painted with acid on a weekly basis until cured. Podophyllin use has several important disadvantages: limited efficacy, potential systemic toxicity, and the need to wash off the tincture in six to eight hours to avoid burns. Podophyllin is also applied on a weekly schedule.

The newest surgical treatment is the carbon dioxide laser. This approach is often chosen when lesions are extensive or refractory to other treatments. Laser therapy usually yields good cosmetic results. On the other hand, the equipment is costly, anesthesia of some type is required (often in an operating room), and careful training and supervision are necessary for a physician learning the technique.

Cryosurgery and electrodesiccation are widely available in physicians' offices, inexpensive, and easy to use. Extensive lesions may require the use of local anesthesia or regional or general anesthesia in an operating room. Scarring and stricture formation are possible complications.

Interferon therapy has attracted interest as another option. Intralesional administration appears to produce fewer systemic reactions than intramuscular injections. A flulike illness associated with administering interferon has seriously limited its use. Randomized clinical trials of interferon are insufficient to establish its possible role in treating genital warts. The Centers for Disease Control suggest that interferon use not be recommended because of its relatively low efficacy, high incidence of toxicity, and high cost.

DAVID A. GRIMES, MD
*Los Angeles*

REFERENCES

Centers for Disease Control: 1989 Sexually Transmitted Diseases Treatment Guidelines. MMWR 1989; 38:18-21

Eron LJ, Judson F, Tucker S, et al: Interferon therapy for condylomata acuminata. N Engl J Med 1986; 315:1059-1064

Krebs HB: Prophylactic topical 5-fluorouracil following treatment of human papillomavirus-associated lesions of the vulva and vagina. Obstet Gynecol 1986; 68:837-841

## Laparoscopic Surgery for Ectopic Pregnancy

LAPAROSCOPIC SURGICAL TREATMENT has become an accepted method for many patients with ectopic pregnancy. Laparoscopic treatment is indicated when the patient has provided informed consent, she is hemodynamically stable, the surgeon has the requisite equipment and operative laparoscopy experience, and intraoperative bleeding can be controlled. Early diagnosis with serial $\beta$-human chorionic gonadotropin (hCG) levels and pelvic ultrasonography increases the feasibility of a laparoscopic approach.

Treatment may involve linear salpingostomy, segmental tubal resection, or salpingectomy. Linear salpingostomy should be done if the ectopic mass is less than 5 cm in the ampulla or 2 cm in the isthmus, the woman desires future fertility, and if the tube retains a reasonable reproductive capability. The operation usually requires two 5-mm lower abdominal puncture sites for instruments. The ectopic pregnancy is exposed with atraumatic tubal grasping forceps. Most but not all surgeons prefer to administer 10 ml of vasopressin (Pitressin), 20 units in 100 ml of a normal saline solution, into the medial proximal mesosalpinx and 10 ml into the lateral distal mesosalpinx. The tube is then opened at the point of maximum bulge, along the antemesenteric border, using a needle electrode, electrocautery unit, and scissors or a carbon dioxide, KTP 532, argon, neodymium:YAG laser. Results are equivalent regardless of the technique. The ectopic pregnancy will slowly extrude over a two-minute interval, after which it can be gently grasped and completely removed. Bleeding usually stops on its own, but vasopressin, bipolar cautery, laser energy, pressure, or, rarely, suturing can also be used. Copious irrigation distally and hydrotubation proximally ensure that the products of conception have been removed. The tubal incision will close by secondary intention. The laparoscopic operating time may initially be longer than that of laparotomy but will shorten as experience is acquired. Segmental resection may be preferred for large isthmic ectopic pregnancies, ruptured ectopic pregnancies, or to control hemorrhage. Salpingectomy is reserved for tubes with pronounced anatomic distortion, for women not desiring future pregnancy, or to control hemorrhage. Bipolar cauterization followed by scissor dissection can be used, or in the case of salpingectomy, loop ligatures can be applied. The products of conception can be removed with a 10-mm Senn forceps.

Women can be discharged within two hours of the operation, to be seen within two days in the office for postoperative care and to measure serum $\beta$-hCG levels. This test should be repeated at one week and thereafter at appropriate intervals until the levels disappear. About 5% to 20% of patients will have persistent $\beta$-hCG titers. Most can be managed by careful observation; a few will require a second operation. The role of chemotherapeutic agents such as methotrexate and RU 486 is being studied.

Patients who have had a salpingectomy have a 50% chance of eventually achieving a viable pregnancy, and those having linear salpingostomy have a 60% to 65% chance. Both have a 10% to 15% probability of a recurrent ectopic pregnancy. A laparoscopic procedure for ectopic pregnancy, therefore, offers comparable or improved results, with a much lesser operative procedure, less morbidity, a shorter recovery time, and reduced cost.

G. DAVID ADAMSON, MD
*Stanford, California*

REFERENCES

Brumsted J, Kessler C, Gibson C, et al: A comparison of laparoscopy and laparotomy for the treatment of ectopic pregnancy. Obstet Gynecol 1988; 71:889-892

Leach RE, Ory SJ: Modern management of ectopic pregnancy. J Reprod Med 1989; 34:324-338

Mecke H, Semm K, Lehmann-Willenbrock E: Results of operative pelviscopy in 202 cases of ectopic pregnancy. Int J Fertil 1989; 34:93-94, 97-100

Vermesh M: Conservative management of ectopic gestation. Fertil Steril 1989; 51:559-567

## Therapeutic Insemination by Donor

THERAPEUTIC INSEMINATION BY DONOR has become widely used to treat male infertility, with between 10,000 and 30,000 births per year resulting from donor insemination. Indications for donor insemination include azoospermia, severe oligospermia, poor motility, abnormal sperm morphology, vasectomy with a poor prognosis for reversal, known genetic disorders in a man, a severely Rh-sensitized woman with an Rh-positive husband, and ejaculatory dysfunction.

Because of increasing concern regarding the possible

transmission of the human immunodeficiency virus (HIV) during donor insemination, the American Fertility Society guidelines for the use of semen-donor inseminations were revised in 1988. It is possible for HIV to be present in fresh donor semen before the donor has become seropositive, a phenomenon that may take three months or longer after infection. Therefore, the use of fresh semen is no longer warranted and only frozen specimens should be used. The frozen specimens are then quarantined for 180 days and the donor retested and found to be seronegative for HIV before the specimen is released for use. Even then the potential for transmission cannot be eliminated.

Lower fecundity rates are reported using frozen semen than with fresh. To achieve the same cumulative pregnancy rates, about twice as many insemination cycles are required to obtain comparable results. This is most likely related to the decreased motility and shorter half-life of cryopreserved sperm than of fresh. Several factors can influence the results of an insemination program using frozen-thawed donor semen. It is not yet clear what number of total motile sperm should be inseminated, but studies have indicated the minimum necessary for acceptable pregnancy rates to be in the range of 20 million. Comparable pregnancy rates to fresh sperm were obtained in one study using 40 million total motile sperm per insemination. The recipient woman's fertility potential also plays an important role, with optimal pregnancy rates occurring when no female infertility factors are present or when a patient's ovulatory dysfunction was corrected with a course of clomiphene citrate. Endometriosis reduces fertility substantially. The route of insemination has traditionally been by the intravaginal or cervical deposition of semen. Controversy exists as to whether improved pregnancy rates might be achieved with intrauterine inseminations. Definitive studies have yet to be completed regarding the efficacy of such a method.

Overall the accepted conception rate per donor insemination cycle is 8% to 10% with a 60% to 70% pregnancy rate by the end of 12 cycles. In addition, no increased risk of miscarriage, ectopic pregnancy, or birth defects has been associated with therapeutic insemination. Couples who fail to attain pregnancy after one year of therapeutic insemination by donor should be counseled on other options including adoption, gamete intrafallopian tube transfer, or in vitro fertilization.

LEE R. HICKOK, MD
*Portland, Oregon*

#### REFERENCES

American Fertility Society: New guidelines for the use of semen donor insemination 1986. Fertil Steril 1986; 49(Suppl):95S-100S

Batzer FR, Corson SL: Indications, techniques, success rates, and pregnancy outcome: New directions with donor insemination. Semin Reprod Endocrinol 1987; 5:45-57

Hummel WP, Talbert LM: Current management of a donor insemination program. Fertil Steril 1989; 51:919-930

## Update on α-Fetoprotein Screening in California

CALIFORNIA LAW REQUIRES that screening for neural tube and certain other birth defects using the maternal serum α-fetoprotein (AFP) level be made available to all pregnant women.

α-Fetoprotein produced by the fetal liver appears in the maternal serum in measurable quantity by the 15th completed week and increases in concentration until term. Maternal serum AFP results are reported as multiples of the median value for a given gestational age and, as such, have provided a number of insights into conditions affecting a fetus, the pregnancy, or both.

The usefulness of maternal serum AFP screening is improved with accurate pregnancy dating and when raw values are adjusted for race, body weight, and the presence of insulin-dependent diabetes mellitus. Maternal serum AFP levels can be raised or lowered by several conditions affecting fetal AFP production or transplacental or amniotic diffusion. These conditions include multiple gestations, fetal demise, and structural defects such as open spina bifida, gastroschisis, and omphalocele. It is necessary, therefore, to carefully examine the pregnancies of women having abnormal serum AFP values. This begins with expert high-resolution ultrasonography to confirm the gestational age and the presence of a single fetus that is viable and has no structural defect. An abnormal elevation unexplained by ultrasonography should have amniotic fluid collected for AFP determination. If the AFP level is elevated, the acetylcholinesterase level, an enzyme specific for neural tissue, is also assayed.

Using this protocol, about 95% of cases of anencephaly, 80% of cases of open spina bifida, and many ventral wall defects could be detected prenatally.

There is also increasing evidence that a high maternal serum AFP level correlates with an adverse pregnancy outcome defined as fetal death, miscarriage, prematurity, or a congenital anomaly other than those described above.

Because fetuses with Down's syndrome on average produce less AFP, low maternal serum levels can be used to identify another high-risk group of pregnancies: those at risk for Down's syndrome. The combination of maternal age (for women younger than 35 at term) and maternal serum AFP multiples of median values can be used to assign specific risk figures. These women also should be offered amniocentesis. Approximately 20% of fetuses with Down's syndrome are detectable by this method.

In California a comprehensive maternal serum AFP screening program has been in operation since April of 1986. Preliminary data reveal that during the first three completed fiscal years, about 640,000 women participated in the program and 39,000 initially had abnormal results. Many corrections were made regarding gestational age and multiple gestations, thus decreasing the number of abnormal results. There were 23,463 women whose pregnancies were evaluated at contracting prenatal diagnosis centers. Of those pregnancies, 947 had fetal abnormalities, including 457 neural tube defects, 182 ventral wall defects, 83 Down's syndrome, 118 other chromosomal abnormalities, and 107 other birth defects. These numbers are likely to increase because additional reports of abnormalities are being reviewed. These include cases diagnosed after abnormal maternal serum AFP results but evaluated outside of the contracted follow-up system.

The California program shows that coordinated efforts of a state health department, genetics experts, local clinicians, and regional laboratories can result in an effective population-wide screening program.

GEORGE CUNNINGHAM, MD
*Berkeley, California*

#### REFERENCES

Lustig L, Clarke S, Cunningham G, et al: California's experience with low MS-AFP results. Am J Med Genet 1988; 31:211-222

Robinson L, Grau P, Crandall BF: Pregnancy outcomes after increasing maternal serum α-fetoprotein levels. Obstet Gynecol 1989; 74:17-20

Wald NJ, Cuckle HS: Recent advances in screening for neural tube defects and Down's syndrome. Baillieres Clin Obstet Gynaecol 1987; 1:649-676

## Testing for Chlamydial Infection

*Chlamydia trachomatis* infection is the most prevalent bacterial sexually transmitted disease in the United States, causing more than 4 million infections annually at a cost of about $2 billion. Although men and infants are also affected, women are at greatest risk for serious complications, including adverse reproductive consequences such as ectopic pregnancy and infertility. To minimize the risk for these tragic outcomes and prevent further transmission, timely diagnosis and appropriate treatment are essential.

Several diagnostic tests for chlamydial infections are now available, but they vary considerably in their cost, reliability, and availability. The two methods currently used to routinely screen for and diagnose chlamydial infection are culture and antigen detection. Culture is considered to be the definitive method of diagnosing a chlamydial infection. This method, however, is expensive—at the time of writing, as much as $30 per test—because isolating *C trachomatis* requires cell culture techniques similar to those used to detect viruses. Moreover, culture requires two to four days before results are available. For these reasons, culture is more widely used by investigators than clinicians.

Two antigen-detection approaches are currently available: direct immunofluorescent staining of smears using monoclonal antibodies, and the detection of chlamydial antigen from swabs measured by enzyme-linked immunosorbent assay (ELISA). Compared with culture, antigen detection is less expensive (cost usually less than a third as much), technically easier, and may provide results within a couple of hours. The two antigen-detection tests most comprehensively evaluated are Microtrak (direct smear test) and Chlamydiazyme (ELISA). Overall, they appear to be of comparable sensitivity and specificity compared with culture, although some data suggest that the direct smear test may have a slightly higher sensitivity in urethral infections in men and specificity in cervical infections. Studies of the direct smear test show the sensitivity ranging from 60% to 100% and specificity ranging from 72% to 99%, depending on the population studied. For the enzyme immunoassay, the sensitivity ranges from 50% to 98% and specificity from 93% to 100%. Both tests appear to be associated with better results in women with cervical infection than in men with urethral infection and in symptomatic patients than in asymptomatic patients, where fewer inclusion-forming units are found. The direct smear test has also been used to detect eye and rectal infections. One distinction between the two antigen-detection tests is how they are processed: The direct smear test is labor-intensive, requiring a high-quality fluorescent microscope and an experienced microscopist, while the ELISA is less labor-intensive and more automated but requires more specialized laboratory equipment (a spectrophotometer).

Serology and cytology are the other two methods of detecting *C trachomatis,* but both are infrequently used in clinical settings. In addition to being a research tool, serology has been used to evaluate infertility in women. Cytologic methods are not routinely used primarily owing to their low sensitivity. Women with Papanicolaou smears suggestive of chlamydial infection should, in particular, receive a confirmatory test—that is, culture or antigen-detection test.

In collecting a specimen to diagnose chlamydial infection, special care should be taken to ensure that the cervical os is cleaned of mucus and debris with a swab before the specimen is obtained and that epithelial cells are collected on specimens obtained by scraping the urethra, cervix, or rectum. Because chlamydiae are obligate intracellular pathogens, specimens obtained from purulent discharges, secretions, or urine are inappropriate. In addition, specimens should be processed as instructed by laboratory protocol. This will, at a minimum, entail immediately placing the specimen in transport medium and providing timely refrigeration.

When chlamydial infection is diagnosed, patients should be treated immediately with an effective regimen. All sex partners should be examined for sexually transmitted disease and also treated promptly for *C trachomatis* with an effective regimen.

A. EUGENE WASHINGTON, MD, MSc
*San Francisco*

### REFERENCES

Centers for Disease Control: *Chlamydia trachomatis* infections—Policy guidelines for prevention and control. MMWR 1985; 34 (Suppl):53S-74S

Centers for Disease Control: 1989 Sexually Transmitted Diseases Treatment Guidelines. MMWR 1989; 38 (Suppl):18-21

Stamm WE: Diagnosis of *Chlamydia trachomatis* genitourinary infections. Ann Intern Med 1988; 108:710-717

ADVISORY PANEL TO THE SECTION ON OBSTETRICS AND GYNECOLOGY

W. BENSON HARER, JR, MD
*Advisory Panel Chair*
*CMA Section Chair*
*CMA Scientific Board Representative*
*San Bernardino*

JOSEPHINE L. VON HERZEN, MD
*CMA Section Secretary*
*San Diego*

CARL J. LEVINSON, MD
*CMA Section Assistant Secretary*
*San Francisco*

ALAN KING, MD
*Loma Linda University*

EMMET LAMB, MD
*Section Editor*
*Stanford University*

FREDERICK W. HANSON, MD
*University of California, Davis*

PHILIP J. DISAIA, MD
*University of California, Irvine*

ROY M. PITKIN, MD
*University of California, Los Angeles*

HOMER CHIN, MD
*University of California, San Diego*

WILLIAM CROMBLEHOLME, MD
*University of California, San Francisco*

RAUL ARTAL, MD
*University of Southern California*

EZRA DAVIDSON, JR, MD
*Charles R. Drew University of Medicine and Science*

GERALD SHEFREN, MD
*Palo Alto*

HAROLD G. BURTON, MD
*Roseville*

EDWARD GOLDSTEIN, MD
*Chula Vista*

EDWARD W. SAVAGE, JR, MD
*Los Angeles*

ROGER E. SCHLESINGER, MD
*Fullerton*

ALAN LASNOVER, MD
*Cupertino*

# Editorials

## Three Possible Futures for Medicine

THESE ARE TIMES of enormous change. Change is occurring almost everywhere. Quite simply, modern science and technology are responsible for the changes that are producing a new and different social, economic, and political world right before our eyes. This can be seen in medicine as well as in society. And the changes that are occurring in both medicine and society are inter-related. When these inter-relationships and interactions are examined, three possible related futures for medicine may be discerned.

One future will surely be *bioscience and hi-tech medicine.* Progress has been spectacular. It has mesmerized both the profession and the public. It has momentum. What may yet be accomplished by bioscience and hi-tech medicine boggles the mind. The possibilities will capture the imagination of medical scientists for a long time to come. But in medicine as in society, progress in science and technology is producing social, economic, and political changes that must be addressed. There are unmistakable signs that society is becoming disillusioned with what is being accomplished in health care, while at the same time generously supporting further scientific and technologic progress in medicine. The conquest of disease and prolongation of life have turned out to produce more illness and disability rather than less and at ever greater and now unacceptable cost. Scientific medicine is not satisfying many patients or much of the public. Patients are expecting better outcomes, and the public is expecting better results for the health dollars spent. Patients are beginning to take their personal care into their own hands, and the public is beginning to move health care itself into the public arena. Physicians are beginning to be viewed more and more as specialized and subspecialized technicians with all the social, economic, and political implications that this entails for the future of the profession. If bioscience and technology are not the end all, then what else may be in the future of medicine? If it is true that patients are expecting better outcomes and the public is expecting better results for their health dollars, then here may be found possibilities for two other futures for medicine.

What affects patient care outcomes besides biologic science and biotechnology? What has been called the "art" of medicine comes to mind. The art deals with such things as human behaviors, attitudes, cultural beliefs, interactions between physician and patient, interactions among health professionals, and the orchestrating of human and health care resources in patient care. This human side of patient care has received less study and attention than it deserves. There is a body of knowledge to be learned, and there are human skills to be acquired by physicians if they are to achieve the best in patient care outcomes and have satisfied patients, families, and third party payers of care. The art of medicine belongs on a par with bioscience and biotechnology as a vital part of modern medicine. Maybe it is time for a more disciplined approach to the neglected art. Perhaps it is time to develop the all-important human side of patient care as a *social science of medical practice,* a new social science that would be rooted in the practice, and with a new focus on all of the human factors that affect patient care outcomes. This could be a second possible future for medicine and perhaps a most important one for the medical profession as modern patient care evolves in today's society.

Then the public is also expecting better health care results for the dollars spent. In a sense the public is in a role somewhat like a patient whose health status is not satisfactory and who needs a physician's help. Perhaps here is an opportunity, or even a need, for yet a third future for medicine, a new role of *medicine as physician to society.* Physicians are citizens with special training and special insights into what constitutes health and illness. They also have highly developed problem-solving skills, especially where the problems are complex and constantly changing. There is a potential for physicians collectively, through their medical societies and associations at various levels, to work with the larger society as they would with a patient, to help diagnose and then work collaboratively with society to treat a health ailment. The process is a familiar one: the chief complaint, history, examination, diagnostic studies, consultations as needed, a working diagnosis, agreement on a treatment plan, implementation of the treatment plan, monitoring of progress, making course corrections as necessary until the problem is solved or an acceptable steady state is reached. The process works in patient care, and, suitably adapted, it should work in societal health care.

It is not too soon to begin thinking about these possible futures of medicine. In the final analysis the role of medicine, and its scope and responsibility, will be determined by society and not by the profession. This has always been the case. But physicians can also influence events in patient care and health care. This also has always been the case. The profession has but to listen to the complaint and then respond with its science, its humanity, and its professional skills. These three possible futures open up new vistas for medicine, which may not be so new after all.

MSMW

## Hypertension in the Elderly

HYPERTENSION IN THE ELDERLY is commanding an increasing amount of attention—not surprisingly, given the upward shift taking place in the age distribution of our society and the epidemiology of elevated arterial pressures. This attention is nicely focused on the many areas surrounding the prevalence, significance, and management of hypertension in the elderly by Whitcomb and Byyny elsewhere in this issue.[1] The phenomenon of simultaneously declining fertility and mortality has led to a demographic transition in which experts foresee a doubling of the population aged 65 or older in the next 30 years. No matter which cutoff point is chosen to define hypertension in older persons, nor the number of measurements used to establish the diagnosis, any pathophysiologic process affecting 40% to 65% of an estimated 50 million persons in our society is a problem of enormous consequence. Prospective epidemiologic studies have established high blood pressure, and in particular high systolic pressure, as the single greatest risk factor in the elderly, except for age itself. Not only is it the strongest predictor of cardiovascular disease, but elderly persons, especially those with hypertension, are less likely to survive a cardiovascular event.

It is somewhat misleading to say that the cause of hypertension in the elderly is unknown. It is no more so than in younger persons given that essential hypertension rarely has its onset in the elderly. Hypertension in the elderly for the most part represents essential hypertension that developed in a younger person and persisted, with or without treatment, among survivors to an older age. Comparison studies of pathophysiology and hemodynamics in young and elderly hypertensive persons that ignore this are fraught with the potential for misleading inferences concerning etiology. A major real difference, of course, is the tendency for the systolic arterial pressure (unlike the diastolic) to continue to rise with age, but the structural factors responsible for this are not unknown. Other differences may only represent the effects of aging per se, or the consequences (adjustments) of chronic diastolic hypertension in survivors coupled with concomitant ischemic heart disease, or both. Only in isolated systolic hypertension, which typically occurs after age 60, can we really talk about differing causes and pathophysiology. For a better understanding of this, it would be of interest to study a group with borderline isolated systolic hypertension, that is, a diastolic blood pressure of less than 90 mm of mercury and a systolic blood pressure of 140 to 159 mm of mercury, in the decade before age 60. From this group will probably come the incident cases of isolated systolic hypertension in subsequent years. This is not to say that the different pathophysiologic profiles in younger and older hypertensive patients are not real or are unimportant. The differences have significant implications for the choice of therapy.

The evaluation of an elderly hypertensive patient involves an accurate determination of the baseline blood pressure and an assessment of possible end-organ damage and relevant concomitant disease. Whitcomb and Byyny appropriately emphasize the need to determine baseline as the average of several readings on more than one occasion and the importance of standing as well as sitting pressures. This is particularly important because of the greater within-individual variability of blood pressure with age. An inadequate number of blood pressure measurements before diagnosis leads both to overestimates of the prevalence in the literature and to overtreatment in practice. Although pseudohypertension has been said to be common in the elderly, studies to date do not instill confidence in this view. A failure to determine baseline pressures properly is probably a greater source of overestimating blood pressure levels than is pseudohypertension. The Osler maneuver need not be routine but reserved for those patients clinically suspected of having pseudohypertension. More important is checking peripheral pulses for signs of atherosclerosis and for signs of left ventricular hypertrophy as part of the assessment for end-organ damage.

Based on the randomized trials of the treatment of diastolic hypertension in the elderly cited by Whitcomb and Byyny, in addition to the studies by the Veterans Administration[2] and by Coope and Warrender,[3] it is rational to conclude that the evidence for a benefit from treatment, at least up to age 80, is as good as in younger patients and for those with diastolic pressures of 95 mm of mercury or greater. In fact, because of the much higher rate of events in the elderly, the same relative reduction (the intervention group versus the control) results in a much greater absolute reduction in cardiovascular morbidity and mortality in elderly compared with younger subjects. This conclusion represents an important recent advancement in our understanding. Just ten years ago an editorial review in the *British Medical Journal* concluded "there is no evidence that treatment that decreases blood pressure alters prognosis in older hypertensives."[4] It is prudent, however, to be cautious in generalizing from clinical trials (where healthier patients tend to be the rule) to practice, where patients may be seen who are more ill or frail.

It is not appropriate to conclude that isolated systolic hypertension should be treated, based either on its known status as a risk factor or on the results from the randomized trials of treated diastolic hypertension. The differing pathophysiology, particularly the known structural vascular abnormalities in the elderly, including a loss of elasticity and atherosclerosis of major vessels, the potentially greater prevalence of both overt and silent ischemia and consequent myocardial dysfunction, raise concerns about potential adverse effects of antihypertensive therapy. Such concerns include the possible impairment of blood flow to vital organs as well as the potential for a compromised quality of life.

In the pilot study for the Systolic Hypertension in the Elderly Program (SHEP) involving 551 elderly subjects with isolated systolic hypertension, treatment with a diuretic was shown to be effective in lowering the systolic blood pressure and was well-tolerated and safe.[5] Although there was an encouraging trend in cardiovascular event reduction, including stroke, it was not statistically significant and there was no reduction in the incidence of either coronary heart disease or total mortality. The pilot study was not designed with the statistical power to address the question of the benefit of therapy, and we must await the results of the full-scale SHEP trial, scheduled for completion in 1991, before making definitive recommendations on the treatment of isolated systolic hypertension. During the interval we must exercise our clinical judgment in making decisions on the treatment of individual patients.

"Individualizing the treatment of hypertension in the elderly, based on clinical characteristics and coexisting conditions," may be even more important than in younger patients.[1] The underlying pathophysiology and hemodynamics favor choosing drugs that lower peripheral vascular resistance and have few central nervous system side effects. In the absence, however, of a specific contraindication or a specific indication for an alternative agent based on a coexisting condition, low-dose diuretics remain the preferred choice in the elderly because they are inexpensive, can be taken once a day, and are of proven long-term benefit.

Angiotensin-converting enzyme inhibitors are effective agents in the elderly, have an excellent quality of life profile, and are a particularly good choice in patients with congestive heart failure or diabetes mellitus. Calcium channel blockers are theoretically an ideal class of antihypertensive agents for the elderly, but definitive comparative data from controlled clinical trials of adequate size are not available. $\beta$-Blockers, central $\alpha$-agonists, and $\alpha_1$-antagonists all have features that relegate them to a lower choice than those discussed above. With all pharmacologic agents for treating the elderly with hypertension, the prudence of starting with very low doses and increasing the dose gradually cannot be stated too often.

The goal or level to which the arterial pressure is lowered may be as important as the choice of agent(s). A J-shaped relationship between the treated level of diastolic pressure and mortality from myocardial infarction has been observed recently in several data sets.[6] Higher rates of myocardial

infarction occurred among those patients with the lowest achieved pressure than in those with more modest lowering. Strandgaard and Haunsø have postulated that the impaired coronary artery reserve, particularly in the subendocardial layer during diastole, resulting from too vigorous lowering of the diastolic blood pressure may explain why antihypertensive treatment protects patients against stroke but not against myocardial infarction.[7] Inconsistencies in the findings among the studies, perhaps due to unknown confounding factors, preclude firm conclusions on this issue at present. Nonetheless, it seems prudent not to be overly aggressive in treating hypertension in elderly patients.

Most of the clinical intervention trials in the elderly with hypertension have shown only modest or no reduction in overall mortality despite reductions in morbidity and mortality rates from cardiovascular disease or stroke, or both. Indeed, sample size considerations may preclude a definitive demonstration of such benefit in the elderly given that age itself is the most powerful risk factor and other competing risks abound. If it is unlikely that life expectancy can be extended significantly, quality-of-life considerations become paramount. Such considerations must include measures of social, emotional, and cognitive functioning and symptoms of the disease or its treatment. For older hypertensive patients, the choice of an antihypertensive regimen least likely to adversely affect the quality of life may be the most important consideration.

WILLIAM McFATE SMITH, MD
*University of California, Berkeley, School of Public Health*
*Department of Epidemiology and International Health*
*University of California, San Francisco, School of Medicine*

**REFERENCES**

1. Whitcomb B, Byyny RL: Perspective on hypertension in the elderly. West J Med 1990; 152:392-400

2. Veterans Administration Cooperative Group: Effects of treatment in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mmHg. JAMA 1970; 213:1143-1152

3. Coope JR, Warrender TS: Randomised trial of treatment of hypertension in elderly patients in primary care. Br Med J (Clin Res) 1986; 293:1146-1151

4. Antihypertensive treatment in the elderly (Editorial). Br Med J 1979; 2:1456-1457

5. Perry HM, Smith WM, McDonald R, et al: Morbidity and mortality in the Systolic Hypertension in the Elderly Program (SHEP) pilot study. Stroke 1989; 20:4-13

6. Berglund G: Goals of antihypertensive therapy—Is there a point beyond which pressure reduction is dangerous? Am J Hypertens 1989; 2:586-593

7. Strandgaard S, Haunsø S: Why does antihypertensive treatment prevent stroke but not myocardial infarction? Lancet 1987; 2:658-661

# Case Reports

## Erythrocytosis Caused by an Erythropoietin-Producing Breast Adenocarcinoma

ROBERT F. BOHNEN, MD
*Roseville, California*

MUSSA BANISADRE, MD
*Modesto, California*

ROLF N. GULBRANDSON, MD
*Roseville, California*

ESMAIL D. ZANJANI, PhD
*Reno, Nevada*

A NUMBER OF NEOPLASMS have been associated with the secretion of erythropoietin and the production of erythrocytosis. The following case report documents the first such association with breast cancer.

### Report of a Case

The patient, a 46-year-old cigarette-smoking woman, noted a right breast mass in 1982 but concealed it from medical attention until February 1984. At this time the center of the breast was missing, the cavity measuring 14 by 7 cm, and nearly all the rest was indurated with neoplasm. Several axillary nodes, as much as 1 cm in diameter, were palpable. Laboratory tests elicited the following values: hematocrit 0.67 (67%), leukocyte count $11.5 \times 10^9$ per liter (11,500 per $\mu$l), and platelet count $200 \times 10^9$ per liter (200,000 per $\mu$l). The red cell volume (chromium 51 method) was increased (2,100 ml, with 1,435 ml predicted), and the plasma volume with radioiodinated serum albumin was normal (2,200 ml, with 2,154 ml predicted). Arterial blood gases include a $Po_2$ of 8.35 kPa (63 mm of mercury), with a carboxyhemoglobin of 0.045 (4.5%), normal being less than 0.037 (3.7%) (study not repeated). An intravenous pyelogram showed a borderline small left kidney at 12.3 cm. Urine catecholamine levels were elevated at 1,375.4 nmol per day (252 $\mu$g per 24 hours), the normal being less than 627.7 nmol per day (115 $\mu$g per 24 hours). Metanephrine values were at the upper limit of normal at 5.5 $\mu$mol per day (1.0 mg per 24 hours). Bone and liver scans did not show distant metastases or splenomegaly.

She had blood pressure readings as high as 208/120 mm of mercury, and her hypertension was treated with hydrochlorothiazide, 25 mg, plus triamterene, 50 mg, given twice a day plus sodium restriction. A biopsy was done that confirmed infiltrating ductal adenocarcinoma. An estrogen-receptor assay was positive at 15 fmol of estradiol bound per milligram of cytosol protein, and a progesterone-receptor assay was negative at 3 fmol of progesterone bound per milligram of cytosol protein. Specimens from the biopsy and peripheral blood serum were sent for erythropoietin assay (see "Methods" section). Both showed elevated levels of erythropoietin, and propranolol hydrochloride, 20 mg three times a day, and methyldopa, 250 mg twice a day, were added for further blood pressure control. Irradiation of 50.4 Gy (5,040 rad) was given to the breast and node-bearing areas. Tamoxifen citrate was also given. The neoplasm shrank, but it was still fixed to the chest wall and centrally ulcerated. She was admitted for a debulking simple mastectomy, with an admission hematocrit of 0.48. The operation was accomplished the end of April 1984. Infiltrating cancer, apparently viable, was present near the deep margins. Pectoral muscle was involved, as were lymphatic vessels. An additional radiation boost of 14 Gy, using electron beams, was given to the whole area. On day 35 after the operation a blood specimen submitted for erythropoietin determination showed that the erythropoietin had fallen to normal levels (see Table 1). Catecholamine levels were still elevated. The tamoxifen therapy was continued.

The patient was admitted to hospital in July 1984 for treatment of a ruptured sigmoid diverticulum with peritonitis. Surgical and antibiotic therapy was successful, and she was discharged without evidence for recurrent neoplasm and without a return of erythrocytosis. She continues to have hypertension but is free of breast cancer recurrence as of July 1987, having a hemoglobin concentration of 134 grams per liter (13.4 grams per dl), a hematocrit of 0.40, no abnormalities on a chemistry panel, and normal chest film and left mammogram at that time, 3½ years after presentation.

### Methods

All specimens were assayed by the exhypoxic polycythemic mouse assay (0.4 atm, 16 hours per day; total 219 hours).[1] Serum was injected as a single dose (1 ml per mouse, 5 mice per group) on day 5 after hypoxia, and radioactive iron (0.5 $\mu$Ci per mouse) was given on day 7. The percent incorporation values of $^{59}$Fe-labeled erythrocytes were determined 72 hours after administering the iron. Values were converted to equivalent units per liter of erythropoietin with references to the standard curve established for the Second International Reference Preparation of erythropoietin.

The tumor tissue (9.2 grams) was homogenized in 32 ml distilled water, freeze-thawed three times, and spun (10,000*g* for 15 minutes) to remove particulate matters. One milliliter extract was given to each assay mouse (5 mice per group) on days 5 and 6 and processed as described. The antierythropoietin antibody used here was prepared in rabbits against partially purified human urinary erythropoietin (3,200 IU per mg potency).[2] The patient's serum and tissue extracts were incubated with the antibody for one hour at 37°C and again at 4°C overnight. Goat anti-rabbit $\gamma$-globulin was added and the mixture incubated for one hour at 37°C and spun at 10,000*g* for 20 minutes to remove precipitates.[2] The supernatants were assayed as above.

(Bohnen RF, Banisadre M, Gulbrandson RN, et al: Erythrocytosis caused by an erythropoietin-producing breast adenocarcinoma. West J Med 1990 Apr; 152:417-418)

From the Departments of Medicine (Drs Bohnen and Banisadre) and Surgery (Dr Gulbrandson), Roseville Community Hospital, Roseville, California, and the Departments of Medicine and Physiology, Veterans Administration Medical Center, Reno, Nevada (Dr Zanjani).

Supported in part by the Veterans Administration, and grant AM 24027 from the National Institutes of Health, Bethesda, Md.

Reprint requests to Robert F. Bohnen, MD, Consultants Medical Group, 406 Sunrise Ave, Roseville, CA 95661.

TABLE 1.—*Erythropoietin Assay Results*

| *Materials Assayed* | *% RBC-$^{59}$Fe Uptake** | *Equivalent U/liter* |
|---|---|---|
| Saline | 0.31 ± 0.04 | ND |
| Erythropoietin | | |
| 50 U | 2.12 ± 0.40 | 50 |
| 200 U | 6.89 ± 0.76 | 200 |
| 800 U | 13.93 ± 1.65 | 800 |
| Normal human serum, female | 0.55 ± 0.12 | ND |
| Patient's serum, before | 9.43 ± 1.10 | 420 |
| Patient's serum, before, plus antierythropoietin | 0.61 ± 0.31 | ND |
| Patient's serum, after | 0.87 ± 0.21 | ND |
| Tissue extract | 5.77 ± 0.87 | 150 |
| Tissue extract plus antierythropoietin | 0.33 ± 0.05 | ND |

ND=not detectable, RBC-$^{59}$Fe=erythrocytes labeled with radioactive iron

*The results from 5 mice per group are given as the mean plus 1 standard error of the mean.

## Discussion

When the patient presented with a high hematocrit and a locally advanced breast cancer, ectopic erythropoietin hormone production was a theoretically possible cause. Leukocyte and platelet counts were normal, the erythrocyte volume was increased, an intravenous pyelogram revealed no renal mass, and a liver-spleen scan was normal. A breast biopsy was needed for estrogen- and progesterone-receptor determinations, and arrangements were made to study erythropoietin values on specimens of blood and biopsy tissue. Both were elevated. She also had hypertension, and catecholamine values were elevated; these findings persisted after irradiation and mastectomy, even though the hematocrit had fallen to 0.40. There is no likely connection between the presence of the two humoral abnormalities.

Neoplasms associated with the ectopic production of erythropoietin include renal cell carcinoma, cerebellar hemangioblastoma, hepatic angiosarcoma, hepatoma, pheochromocytoma, large renal cysts, uterine fibromyoma, and tumors of the thymus, lung, adrenals and ovaries.[3-10] As in the present study, the increased production of erythropoietin in most of these cases was documented using the polycythemic mouse assay, which provides a quantitative evaluation of biologically active erythropoietin from human and animal sources.[5-9] Although the polycythemic mouse assay is relatively insensitive and cannot reliably detect erythropoietin levels below 50 U per liter, erythropoietin levels in patients with tumor-associated erythrocytosis have been generally high—420 U per liter in this patient—and easily detectable. The radioimmunoassay for erythropoietin,[11] now available from commercial sources, is a more sensitive assay procedure and can be used to assess physiologically significant changes in erythropoietin production in clinical disorders of erythropoiesis. We have not been able to find any previous reports in the literature of a primary breast cancer associated with erythrocytosis. Although some fall in the hemoglobin and hematocrit levels due to radiotherapy of the chest wall would be expected, this should in fact result in an increase of the level of erythropoietin and not a diminution as occurred in this patient. Therefore, a fall in both the hematocrit and erythropoietin to normal levels after eradication of the tumor by irradiation and surgical therapy strongly suggests that the breast cancer in this patient was the source of the excessive erythropoietin production. This is further reinforced by the presence of large amounts of erythropoietin in the neoplastic tissue as found by our assays.

Adenocarcinoma of the breast should be added to the list of neoplasms to be considered in the differential diagnosis of unexplained or "inappropriate" erythrocytosis.

### REFERENCES


1. Zanjani ED, Ascensao JL, McGlave PB, et al: Studies on the liver to kidney switch of erythropoietin production. J Clin Invest 1981; 67:1183-1188
2. Zanjani ED, Lutton JD, Hoffman R, et al: Erythroid colony formation by polycythemia vera bone marrow: Dependence on erythropoietin. J Clin Invest 1988; 59:841-848
3. Wintrobe MM, Lee GR, Boggs DR, et al: Polycythemia, chap 30, *In* Clinical Hematology, 7th Ed. Philadelphia, Lea & Febiger, 1974, pp 986-987
4. Erslev AJ: Secondary polycythemia (Erythrocytosis), chap 73, *In* Williams WJ, Beutler E, Erslev AJ, et al (Eds): Hematology, 3rd Ed. New York, McGraw-Hill, 1983, pp 678-680
5. Spivak JL: Erythrocytosis and polycythemia, chap 9, *In* Spittell JA Jr (Ed): Clinical Medicine—Vol 5, Hematology/Pulmonary Disease. Philadelphia, Harper & Row, 1986, pp 1-7
6. Lipsett MB: Hormonal syndromes associated with neoplasia, chap 3, *In* Levine R, Luft R (Eds): Advances in Metabolic Disorders. New York, Academic Press, 1968, pp 131-133
7. Sachs BA: Endocrine disorders produced by nonendocrine malignant tumors. Bull N Y Acad Med 1965; 41:1069-1086
8. Omenn GS: Ectopic hormone syndromes associated with tumors in childhood. Pediatrics 1971; 47:613-622
9. Anagnostou A, Chawla MS, Pololi L, et al: Determination of plasma erythropoietin levels—An early marker of tumor activity. Cancer 1979; 44:1014-1016
10. Ossias AL, Zanjani ED, Zalusky R, et al: Studies on the mechanism of erythrocytosis associated with a uterine fibromyoma. Br J Haematol 1973; 25:179-185
11. Clemons GK: Comparison of radioimmunoassay and bioassay of erythropoietin, chap 29, *In* Zanjani ED, Tavassoli M, Ascensao JL (Eds): Regulation of Erythropoiesis. Great Neck, NY, PMA Publishing, 1988, pp 363-374


# Prenatal Diagnosis of Noonan's Syndrome in a Female Infant With Spontaneous Resolution of Cystic Hygroma and Hydrops


LUIS IZQUIERDO, MD
ORI KUSHNIR, MD
DIANE SANCHEZ, MD
LUIS CURET, MD
PATRICIA OLNEY, MS
GLORIA E. SARTO, MD, PhD
CAROL CLERICUZIO, MD
*Albuquerque*

RICHARD OLNEY, MD
*Gallup, New Mexico*


THE NOONAN SYNDROME is one of multiple congenital anomalies that may occur on a sporadic basis or in a pattern consistent with an autosomal dominant inheritance.[1,2] The pathogenesis remains unknown and the expression is variable.[1,2] It has been associated with a spectrum of congenital abnormalities. Some of the phenotypic malformations include ptosis, pterygium colli, cryptorchidism, short stature, heart defect, and the jugular obstructive lymphatic sequence.[1,2]

Cystic hygromas are congenital malformations of the


(Izquierdo L, Kushnir O, Sanchez D, et al: Prenatal diagnosis of Noonan's syndrome in a female infant with spontaneous resolution of cystic hygroma and hydrops. West J Med 1990 Apr; 152:418-421)



From the Departments of Obstetrics and Gynecology (Dr Izquierdo, Dr Kushnir, Dr Sanchez, Dr Curet, Ms Olney, and Dr Sarto) and Pediatrics (Dr Clericuzio), University of New Mexico Hospital, Albuquerque, and the Department of Pediatrics, Gallup Indian Medical Center, Gallup, New Mexico (Dr Olney).

Reprint requests to Luis Izquierdo, MD, Department of Obstetrics and Gynecology, University of New Mexico School of Medicine, 2211 Lomas Blvd NE, Albuquerque, NM 87131.

lymphatic system that appear as fluid-filled cavities most commonly found in the posterior cervical area.[3,4] Posterior cervical hygroma is a rather nonspecific malformation found in a number of unrelated conditions that reflects a failure or delay in the development of the connection between the jugular lymph sac and the internal jugular vein.[4] Frequently cystic hygromas are found in association with chromosomal aberrations.[3,5] When cytogenetic studies are normal, Noonan's syndrome should be included in the differential diagnosis.[4,6-8] We report a case of Noonan's syndrome in a female fetus accompanied by the spontaneous resolution of a fetal cystic hygroma and hydrops, and followed by the delivery of a term live-born infant.

## Report of a Case

The patient, a 19-year-old gravida 1, para 0 woman at 29 weeks' gestation, was referred to the High Risk Obstetrical Unit at the University of New Mexico, Albuquerque, for preterm labor. An ultrasonogram done on admission revealed a single living fetus with a biparietal diameter of 73 mm, an abdominal circumference of 255 mm, and a femur length of 56 mm, all consistent with an estimated fetal age of 28 to 29 weeks. Also noted on this ultrasound examination was a large, cystic, septated nuchal mass (Figure 1), accompanied by generalized fetal edema, including scalp edema, pericardial effusion, and ascites (Figure 2). A diagnosis of cystic hygroma with hydrops was made. The patient was Rh-positive and had a negative indirect Coombs test. Fetal echocardiography was normal. The medical and family histories were unremarkable. A genetic history and the family pedigree were obtained, showing no evidence of previous anomalies in the family.

The patient received tocolytic therapy with terbutaline sulfate. After contractions subsided, an ultrasonogram was again done. No other structural anomalies were observed. The family was informed about the risks of chromosomal abnormalities. An amniocentesis for culture of amniotic fluid cells was done, a 46,XX karyotype determined, and 15 metaphases of 46 chromosomes were counted, with 5 being completely analyzed.

The patient was discharged home and was thereafter observed at her primary care facility. She returned to our clinic at 36 weeks and 6 days of gestation. On ultrasonogram the cystic hygroma had spontaneously disappeared, leaving only redundant skin and edema in the posterior cervical area. The hydrops had also resolved.

At 39 weeks, the patient went into active labor and was delivered of a single, living female child vaginally; Apgar

**Figure 1.**—An ultrasonogram view of the posterior craniocervical area of the fetus shows a large, cystic, septated mass.

**Figure 2.**—A transverse section of the abdomen of the fetus shows ascites.

**Figure 3.**—The neonate after delivery shows evidence of pterygium colli and a low hairline.

Figure 4.—Generalized lymphedema of feet and laxity of the abdominal wall are seen.

scores were 8 and 9 at one and five minutes, respectively. The infant weighed 3,140 grams (50th percentile).

Examination of the newborn by pediatricians and dysmorphologists showed the following: pterygium colli, generalized lymphedema of the hands, feet, and genitals (Figures 3 and 4), a low posterior hairline, and widely spaced nipples. A heart murmur was heard over the pulmonary valve area during systole, highly suggestive of pulmonary stenosis, and echocardiography was done. All these findings were consistent with Noonan's syndrome.

Cytogenetic studies of the infant's blood confirmed the 46,XX karyotype, with 20 metaphases of 46 chromosomes being counted and 10 analyzed completely.

## Discussion

In the fetus, the lymphatic system drains into the jugular lymphatic sac. If the connection between the jugular vein and the lymphatic system does not occur (around 40 days of gestation), progressive peripheral lymphedema, hydrops, and cystic hygroma will develop.[3,5,9] This phenotype is recognized as the jugular lymphatic obstructive sequence.[10(pp472-473)] If the connection is subsequently formed, this sequence is interrupted, with resultant reabsorption of the fluid collections. A residual effect is a webbed neck (pterygium colli) due to redundant skin. Other consequences of overdistention of the jugular lymphatic sac are uplifting and anterior rotation of the ears with abnormal hair patterns. The peripheral lymphedema gives rise to redundancy of the skin of the face and puffy hands and feet.[5] Laxity of the ventral wall as a result of ascites has also been reported.[10(pp472-473)]

Cystic hygromas can be diagnosed by ultrasonography.[3-8,11-14] Characteristically, they present as posterolateral cystic masses having a midline septum. The skull and spine are intact and there are no solid components in the mass.[3] The differential diagnosis includes cervical meningoceles, encephaloceles, neck tumors, and nuchal edema.[5]

Previous studies have shown that the prenatal diagnosis of cystic hygroma and hydrops is associated with a poor prognosis irrespective of karyotype.[3,5] Romero and co-workers reviewed 40 cases reported in the literature, most of them involving hydrops, and 33% of infants died in utero, usually within a few weeks of the diagnosis, 5% died in the early neonatal period, and the rest were electively aborted. Still further evidence of a poor prognosis irrespective of karyotype in cases of cystic hygroma and hydrops was presented in 1989 by Abramowicz and colleagues at the Society of Perinatal Obstetricians in which only one of six fetuses with a normal karyotype survived.[15] Prognostic data on fetal cystic hygromas without associated hydrops are scanty.[5]

In Noonan's syndrome, the features of nuchal cystic masses and nonimmune hydrops have been identified by ultrasonography.[2,6-8,14] Additional information rendered by fetal echocardiography is a possible diagnosis of pulmonary valve stenosis.[1,2] Review of the literature reflects variable findings on amniotic fluid $\alpha$-fetoprotein levels in the presence of cystic hygroma; some investigators report elevated levels whereas others report normal levels.[2,12]

In cases in which chromosome abnormalities, including monosomy or trisomy, are associated with cystic hygroma and hydrops, the recurrence risk will be low; chorionic villus sampling or amniocentesis, however, should be offered in subsequent pregnancies.[12] When chromosomal studies are normal, as in the Noonan syndrome, an autosomal dominant inheritance with a variable penetrance trait should be considered. In cases of Noonan's syndrome, monitoring of future pregnancies with ultrasonography and possibly fetal karyotyping should be suggested to provide reassurance to the family.[3]

Determination of the fetal karyotype should be recommended in all cases of cystic hygroma and hydrops. If the karyotype is normal, appropriate immunologic and viral studies are required and may be useful for counseling in the future.[5] Pregnancy interruption should be offered before viability,[5] although in patients with a normal karyotype the progression of the hygroma should be followed by ultrasonogram as the outcome may be normal.[8] After viability is reached, because of the dire prognosis, fetuses with hydrops should probably be managed nonaggressively.[5] A thorough search for associated anomalies must be done after delivery to corroborate the prenatal diagnostic findings.[13]

This case report supports the importance of including the Noonan syndrome in the differential diagnosis of fetal cystic hygroma and hydrops. It describes a fetus with spontaneous resolution of the jugular lymphatic obstructive sequence, who reached viability and was delivered at term, contrary to and different from most published reports.

This supports the consideration that fetuses with normal chromosomal studies and normal echocardiography, in the presence of cystic hygroma and hydrops, could be managed expectantly if the family desired to continue with the pregnancy.[8,14]

Furthermore, based on our personal observations and those of others, decompression of cystic hygromas guided by ultrasonography should be considered as an option for further investigation of these fetuses. Successful fetal karyotyping in cases of fetal cystic hygroma and oligohydramnios can be done from the hygroma fluid using standard culture techniques.[16]

### REFERENCES

1. Mendez HMM, Opitz JM: Noonan syndrome: A review. Am J Med Genet 1985; 21:493-506

2. Witt DR, Hoyme HE, Zonana J, et al: Lymphedema in Noonan syndrome: Clues to pathogenesis and prenatal diagnosis and review of the literature. Am J Med Genet 1987; 27:841-856

3. Chervenak FA, Isaacson G, Blakemore KJ, et al: Fetal cystic hygroma—Cause and natural history. N Engl J Med 1983; 309:822-825

4. Kalousek DK, Seller MJ: Differential diagnosis of posterior cervical hygroma in previable fetuses. Am J Med Genet (Suppl) 1987; 3:83-92

5. Romero R, Pilu G, Jeanty P, et al: Prenatal Diagnosis of Congenital Anomalies. Norwalk, Conn, Appleton & Lange, 1988, pp 115-118

6. Benacerraf BR, Greene MF, Holmes LB: The prenatal sonographic features of Noonan's syndrome. J Ultrasound Med 1989; 8:59-63

7. Zarabi M, Mieckowski GC, Mazer J: Cystic hygroma associated with Noonan's syndrome. JCU 1983; 11:398-400

8. Macken MB, Grantmyre EB, Vincer MJ: Regression of nuchal cystic hygroma in utero. J Ultrasound Med 1989; 8:101-103

9. Brace RA: Effects of outflow pressure on fetal lymph flow. Am J Obstet Gynecol 1989; 160:494-497

10. Smith DW, Jones KL: Recognizable Patterns of Human Malformation: Genetic, Embryologic and Clinical Aspects, 3rd Ed. Philadelphia, WB Saunders, 1984

11. Garden AS, Benzie RJ, Miskin M, et al: Fetal cystic hygroma colli: Antenatal diagnosis, significance, and management. Am J Obstet Gynecol 1986; 154:221-225

12. Pijpers L, Reuss A, Stewart PA, et al: Fetal cystic hygroma: Prenatal diagnosis and management. Obstet Gynecol 1988; 72:223-224

13. Mostello DJ, Bofinger MK, Siddigi TA: Spontaneous resolution of fetal cystic hygroma and hydrops in Turner's syndrome. Obstet Gynecol 1989; 73:862-865

14. Distell BM, Hertzberg BS, Bowie JD: Spontaneous resolution of a cystic neck mass in a fetus with normal karyotype. AJR 1989; 153:380-382

15. Abramowicz JS, Warsof SL, Levy DL: Prenatal Diagnosis of Congenital Cystic Hygroma: Poor Prognosis, Irrespective of Karyotype. Presented at the 9th annual meeting of the Society of Perinatal Obstetricians, New Orleans, February 1989 (Abstract 167)

16. Von Oegen PT, Kirk J, Comstock CH, et al: Successful Fetal Karyotyping from Cystic Hygroma Fluid. Presented at the 9th annual meeting of the Society of Perinatal Obstetricians, New Orleans, February 1989 (Abstract 179)

# Chylothorax and Respiratory Failure in Kaposi's Sarcoma

DANIEL W. PENNINGTON, MD
MARTHA L. WARNOCK, MD
MICHAEL S. STULBARG, MD
*San Francisco*

DISSEMINATED KAPOSI'S SARCOMA (KS) is a common problem in patients with the acquired immunodeficiency syndrome, particularly in homosexual men. Intrathoracic involvement occurs clinically in as many as a fifth of patients with KS[1,2] and has been reported in 11 of 23 consecutive patients in an autopsy series.[3] Pulmonary KS usually, though not always, follows the appearance of characteristic lesions on the skin. Its clinical and radiographic presentation may mimic pneumonia due to opportunistic infections, although nodular infiltrates and intrathoracic lymph node enlargement are commonly seen. Pleural effusions occur in as many as half of patients with pulmonary KS; they may be bilateral and are often hemorrhagic. Although they result from tumor implants on the visceral pleura, neither cytologic examination of the fluid nor pleural biopsies are helpful in establishing the diagnosis.[3-5] Because pleural effusions only rarely occur in patients with *Pneumocystis carinii* pneumonia or other opportunistic infections, the presence of a pleural effusion in a patient with cutaneous KS suggests the diagnosis of pulmonary KS.[4] Among patients with pulmonary KS, those with pleural effusions have substantially shortened survival.[6] Chylous pleural effusions, on the other hand, have been reported previously in only two patients with KS.[7,8]

(Pennington DW, Warnock ML, Stulbarg MS: Chylothorax and respiratory failure in Kaposi's sarcoma. West J Med 1990 Apr; 152:421-422)

From the Departments of Medicine (Drs Pennington and Stulbarg) and Pathology (Dr Warnock), Cardiovascular Research Institute (Dr Pennington), University of California, San Francisco, School of Medicine.

Reprint requests to Daniel W. Pennington, MD, Box 0130, Cardiovascular Research Institute, UCSF, Third and Parnassus, San Francisco, CA 94143.

ABBREVIATIONS USED IN TEXT
CT = computed tomographic
KS = Kaposi's sarcoma

## Report of a Case

The patient, a 35-year-old homosexual man, had violaceous skin lesions develop in early 1986, and a skin biopsy in June of that year disclosed Kaposi's sarcoma. Although he had no pulmonary symptoms, a diffuse, interstitial pulmonary infiltrate was noted, and an opportunistic infection was suspected. Over the next six months, bronchoalveolar lavage was done on three occasions, but no diagnosis was established.

In February 1987, the patient was admitted to the hospital with chills and sweats. On examination he had many cutaneous KS lesions and enlarged left axillary and right submandibular lymph nodes. A chest radiograph revealed a diffuse pulmonary interstitial infiltrate and blunting of the right costophrenic angle, suggesting a small pleural effusion. The patient refused a diagnostic evaluation and was discharged against medical advice.

The patient was admitted again in April 1987 because of

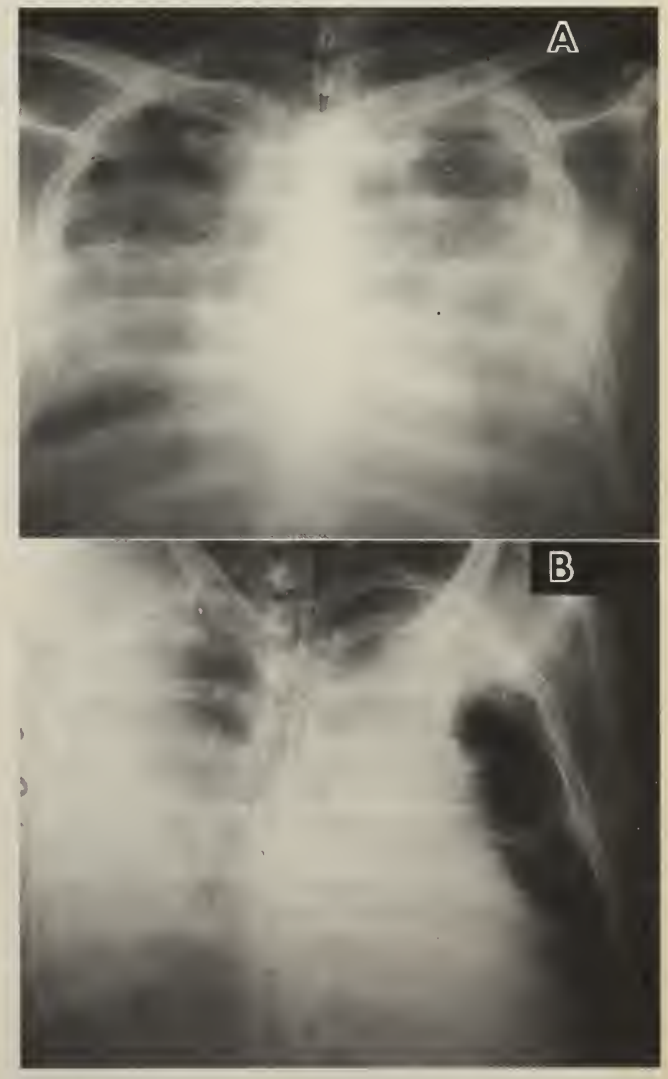



**Figure 1.—A,** Anteroposterior and, **B,** right-side-down decubitus chest films show bilateral large pleural effusions.

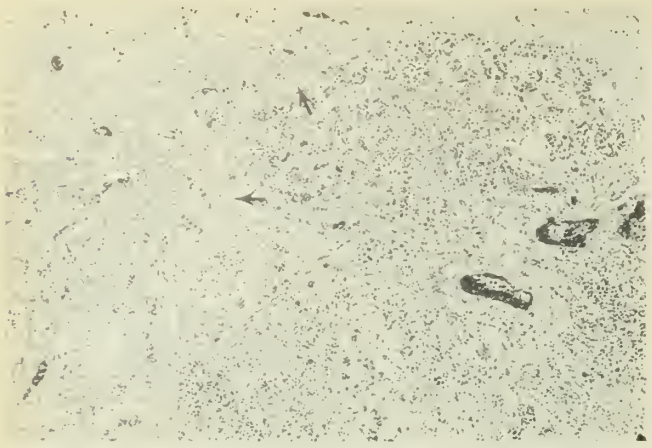


**Figure 2.**—A photomicrograph of a mediastinal lymph node shows involvement of the capsule **(top)** and invasion of nodal parenchyma by the vascular interlacing spindled cells of Kaposi's sarcoma **(arrows)** (hematoxylin and eosin; original magnification × 80).

abdominal pain; a computed tomographic (CT) scan revealed the presence of small bilateral pleural effusions that were not detected on chest radiograph. During abdominal exploration he was found to have diffuse violaceous lesions, with notably enlarged spleen and lymph nodes. Biopsies were taken of three para-aortic lymph nodes, and all showed Kaposi's sarcoma. Purulent peritonitis with *Staphylococcus aureus* bacteremia and wound dehiscence developed postoperatively. His pleural effusions progressively enlarged; at the same time, anasarca developed and he had severe malnutrition with a serum albumin level of less than 20 grams per liter. Twenty-one days after laparotomy he suffered a respiratory arrest that was attributed to large pleural effusions (Figure 1). He required mechanical ventilation, and thoracentesis removed 500 ml of fluid from the left pleural space. His ventilation improved, and the endotracheal tube was removed. During the next week he underwent thoracentesis five times, with obvious but transient improvement in his ventilation each time. The fluid was cloudy on four occasions and serosanguineous once. The protein concentration in the pleural fluid was 30 to 50 grams per liter, the leukocyte count was 200 to 500 × $10^6$ per liter, and the triglyceride concentration was 1.93 mmol per liter (171 mg per dl). A cytologic examination showed no abnormalities. He refused a chest tube placement. No chest pain was reported. His clinical condition deteriorated, and he died on the 42nd hospital day.

An autopsy examination of the chest revealed bilateral serosanguineous pleural effusions: 1,300 ml in the right pleural space and 600 ml in the left. A red-brown macule was noted on the left parietal pleura and was not examined histologically. There were violaceous macules in the airways. Mediastinal lymph nodes were enlarged, firm, and matted together. Sectioning of the nodes revealed hyperemic gray parenchyma, and microscopic examination of pretracheal and carinal nodes showed Kaposi's sarcoma (Figure 2). There was no evidence of an opportunistic infection.

## Discussion

Chylothorax is caused by disruption or obstruction of the thoracic duct. An acute onset of pleural effusion and the presence of turbid pleural fluid that does not clear when centrifuged or that contains at least 1.24 mmol per liter (110 mg per dl) triglyceride establish the diagnosis.[9] Neoplasms are the commonest cause of chylothorax; most of the rest are due to trauma, including surgical procedures. Among tumors, lymphomas and bronchogenic or gastric carcinomas are most often responsible.[10] It is thought that invasion of lymph nodes along the course of the thoracic duct results in interruption of the duct and subsequent chylothorax. Here we report the first case of chylothorax due to Kaposi's sarcoma with documented neoplastic involvement of mediastinal lymph nodes.

Two patients with intrathoracic KS have been reported in whom massive chylous pleural effusions developed.[7,8] There was no evidence of mediastinal adenopathy by CT examination in either case, and the cause of the chylous effusions was unknown.

The patient reported here had documented involvement of mediastinal lymph nodes with Kaposi's sarcoma. No attempt was made at autopsy to find a disruption or obstruction in the thoracic duct; the presence of neoplastic involvement in the nodes, however, strongly suggests that such a disruption or obstruction occurred. The chylous nature of the pleural effusions is confirmed by the elevated triglyceride concentration.[9] The fluid was grossly chylous only intermittently; this may have been due to his severe malnutrition because the presence of chyle in the thoracic duct depends on oral fat intake. It has been reported previously that chylous pleural effusions (defined by the presence of chylomicrons in the fluid) were often described grossly as "bloody" or "yellow turbid" rather than chylous.[9]

Recognizing the diagnosis of chylothorax in patients with Kaposi's sarcoma is important because morbidity may be substantial and treatment may be beneficial. In addition to the problem of ventilatory compromise due to the accumulation of pleural fluid, as seen in this patient, severe malnutrition and immune dysfunction result from the loss of large amounts of protein, fat, and lymphocytes by repeated thoracentesis or chest tube drainage. Bowel rest and total parenteral nutrition may be necessary to reduce the flow of chyle and to nourish the patient adequately. Pleurodesis with a sclerosing agent such as tetracycline may help to limit fluid accumulation and protein and fat losses. Although no satisfactory treatment of pulmonary KS exists, radiation therapy has been used with limited success.[1] In addition, mediastinal irradiation is helpful in controlling chylothorax due to lymphoma and carcinoma. Thus, radiation therapy should be considered in cases of chylothorax due to Kaposi's sarcoma.

### REFERENCES


1. Ognibene FP, Steis RG, Macher AM, et al: Kaposi's sarcoma causing pulmonary infiltrates and respiratory failure in the acquired immunodeficiency syndrome. Ann Intern Med 1985; 102:471-475
2. Garay S, Belenko M, Fazzini E, et al: Pulmonary manifestations of Kaposi's sarcoma. Chest 1987; 91:39-43
3. Meduri GU, Stover DE, Lee M, et al: Pulmonary Kaposi's sarcoma in the acquired immune deficiency syndrome. Am J Med 1986; 81:11-18
4. Zibrak JD, Silvestri RC, Costello P, et al: Bronchoscopic and radiologic features of Kaposi's sarcoma involving the respiratory system. Chest 1986; 90:476-479
5. Ognibene FP, Shelhamer JH: Kaposi's sarcoma. Clin Chest Med 1988; 9:459-465
6. Gill P, Akil B, Colletti P, et al: Pulmonary Kaposi's sarcoma: Clinical findings and results of therapy. Am J Med 1989; 87:57-61
7. Schulman LL, Grimes MM: Metastatic Kaposi's sarcoma and bilateral chylothorax. NY State J Med 1986; 86:205-206
8. Pandya K, Lal C, Tuchschmidt J, et al: Bilateral chylothorax with pulmonary Kaposi's sarcoma. Chest 1988; 94:1316-1317
9. Staats BA, Ellefson R, Budahn L, et al: The lipoprotein profile of chylous and nonchylous pleural effusions. Mayo Clin Proc 1980; 55:700-704
10. Light RW: Chylothorax and pseudochylothorax, chap 21, *In* Pleural Diseases. Philadelphia, Lea & Febiger, 1983, pp 209-219

# Fatal Pulmonary Infection With *Mycobacterium fortuitum*

JOSEPH M. NUSSBAUM, MD
P.N.R. HESELTINE, MD
*Los Angeles*

THE ISOLATION OF MYCOBACTERIA of Runyon's group IV from the sputum of patients with pulmonary disorders frequently presents clinicians with difficulty in interpreting the significance of this finding. Numerous case reports in the literature document the identification of these organisms in patients with chronic pulmonary disease, but the pathogenic role of these mycobacteria in an individual patient's clinical course is often unclear.[1-6] In the case presented here, *Mycobacterium fortuitum* was confirmed as the cause of the patient's progressive and ultimately fatal pulmonary disease.

## Report of a Case

The patient, 45 years old at the time of his last admission to Los Angeles County-University of Southern California Medical Center, was an unemployed man who had lived in a succession of boarding houses and was diagnosed as having paranoid schizophrenia. For the past two years, he had progressive dyspnea on exertion and a chronic productive cough. He had recently noted scant hemoptysis, fevers, and an unquantified weight loss. He did not have night sweats. During the month before his last admission, modest pedal edema developed, and he was dyspneic with even minimal exertion. He said he did not have orthopnea, chest pain, or symptoms of gastroesophageal reflux. He was taking no medications.

His past history was significant for pulmonary disease with *Mycobacterium tuberculosis* in June 1983, five years before this admission. The organism was sensitive to all drugs tested. He received supervised therapy for nine months through the Los Angeles County Public Health Department, and his case was closed in May 1984 after repeatedly negative sputum smears and cultures and stabilization of the disease on serial chest roentgenograms. He said he had not had occupational dust exposure or surgery of any kind and did not abuse alcohol or take recreational drugs. He had smoked less than ten pack-years.

A review of his medical records revealed several visits to the emergency department during the previous two years for complaints of cough and dyspnea. He had been briefly admitted on several occasions with the provisional diagnosis of reactivated pulmonary tuberculosis. He was repeatedly given antituberculous medications and referred to the public health department but invariably failed to follow up or continue taking any medicine once discharged. Tracing efforts by the public health department were fruitless as the patient moved frequently.

(Nussbaum JM, Heseltine PNR: Fatal pulmonary infection with *Mycobacterium fortuitum*. West J Med 1990 Apr; 152:423-425)

From the Department of Internal Medicine, Section of Infectious Disease, Los Angeles County-University of Southern California Medical Center.

Reprint requests to Joseph M. Nussbaum, MD, LAC-USC Medical Center, Section of Infectious Disease, General Hospital Rm 6442, 1200 N State St, Los Angeles, CA 90033.

On physical examination with the patient lying supine in bed, he was cachectic and appeared older than his stated age. A specimen cup at the bedside was filled with purulent sputum. The patient became breathless with minimal activity or prolonged conversation. He was notably guarded and evasive in his replies. His pulse was 105 beats per minute, respirations 36 per minute, blood pressure 90/60 mm of mercury without orthostatic changes, and his maximum temperature was 38.9°C (102°F). His height was 172 cm (68 in), his weight 45.4 kg (100 lb). He had poor dentition. His jugular venous pressure was 3 cm above the level of the right atrium. A few rhonchi were audible on auscultation of the lungs, and accessory muscle use was noted during respiration. Cardiac auscultation revealed the $S_1$ to be loud, the pulmonic component of $S_2$ was audible even at the apex, and a soft midsystolic murmur without radiation was heard at the lower left sternal border that did not vary with position or straining. The abdomen was normal. Clubbing was noted of both upper and lower extremities, and there was minimal pitting ankle edema. An arterial blood gas determination while the patient was receiving supplemental oxygen by nasal cannula at 3 liters per minute revealed a $Po_2$ of 79 mm of mercury, a $Pco_2$ of 55 mm of mercury, a pH of 7.37, and a bicarbonate concentration of 31 mEq per liter. The leukocyte count was $9.1 \times 10^9$ per liter with 0.65 segmented neutrophils, 0.12 band forms, 0.15 lymphocytes, 0.07 mononuclear leukocytes, and 0.01 eosinophils. The hemoglobin was 97 grams per liter. An enzyme-linked immunosorbent assay test for antibody to the human immunodeficiency virus was negative. A sputum Gram's stain showed a variety of bacteria without a predominant organism; culture yielded only a mixture of oral saprophytes.

A total of 33 sputum specimens had been cultured for mycobacteria during the 16 months preceding and including this admission: 9 specimens had no mycobacteria recovered on culture; 24 yielded only *Mycobacterium fortuitum* on culture; and 17 specimens obtained on each admission, including the present, yielded 2+ or greater growth. Mycobacteria were identified as *M fortuitum* in the following manner. The growth of acid-fast bacilli was consistently visible within two weeks of incubation on Lowenstein-Jensen media and on nutrient agar in seven days as raised, buff-colored, rough colonies. Growth occurred at 25°C, 32°C, and 35°C, and in salt-containing media, but not at 42°C. The organisms were always negative for niacin production and positive for nitrate reduction, with positive reactions for arylsulfatase and urea, a negative reaction for polysorbate (Tween) hydrolysis, and possessed high catalase activity. All primary cultures were held for a minimum of four weeks and reexamined at weekly intervals to exclude the possibility of a mixed mycobacterial infection. Serial chest roentgenograms for the past 31 months, from the end of his antituberculous treatment up to and including the present admission, are presented (Figure 1). Progressive volume loss, contraction, and cavitation of both upper lung zones, with the appearance of a round, central density consistent with a fungus ball in the left upper lobe cavity, is visible over this period.

Treatment with ethambutol hydrochloride, ethionamide and cefoxitin sodium was given. On his fifth hospital day, the patient refused further tests and treatments and said he wished to leave the hospital. He was discharged to a board-and-care house, and he died suddenly that evening. At au-

topsy, a multitude of caseating granulomas were found in the lungs, thoracic and abdominal lymph nodes, spleen, and liver. Several large cavities were found in both upper lobes, the largest being 8 cm in diameter. Several cavities contained mycetomas identified morphologically as *Aspergillus* species. The right major bronchus and trachea were filled with blood. The heart and esophagus were entirely normal. Culture of a lung specimen obtained at autopsy yielded only *M fortuitum.*

## Discussion

*Mycobacterium fortuitum* has frequently been identified in the sputum of patients with and without pulmonary disease.[1-5,7-10] Many of the earlier cases shared the flaw that the causal relationship between *M fortuitum* and the patient's disease was often questionable.[6] Later reports have usually included data that would allow such a relationship to be more strongly inferred; specifically, repeated isolation over time of the organism, the histologic finding of tissue destruction and granulomatous inflammation, an absence of any other pathologic finding sufficient to account for the patient's pulmonary disease, and the exclusion of *M tuberculosis.* Common to these reports has been the presence of an underlying disorder that seems a necessary precondition for *M fortuitum* to become invasive. Such conditions most commonly have included esophageal disease leading to repeated aspiration, mineral oil pneumonitis, chronic granulomatous disease, rheumatoid arthritis, or ankylosing spondylitis.[7,8,10,11] The present case is unique in that not only was the organism repeatedly identified in the patient's sputum, but serial radiographs document progressive lung destruction, accompanied by hypercapnia, clubbing, and pulmonary hypertension, and there was histologic evidence at autopsy that the patient's disease was both consistent with and due solely to *M fortuitum.* It is unlikely that the patient had a relapse of *M tuberculosis* that was missed because of an overgrowth by *M fortuitum,* as specific precautions against this possibility were observed during the repeated laboratory isolation of mycobacteria from sputum specimens. The only predisposing factors in this case seemed to be the residua of previous pulmonary tuberculosis and malnutrition. Malnutrition has long been recognized as immunosuppressive and certainly contributed to this patient's outcome; whether his malnutrition was the cause or consequence of his progressive mycobacterial disease is uncertain. Our report substantiates that even in a relatively normal host, *Mycobacterium fortuitum* can produce progressive, fatal pulmonary disease.

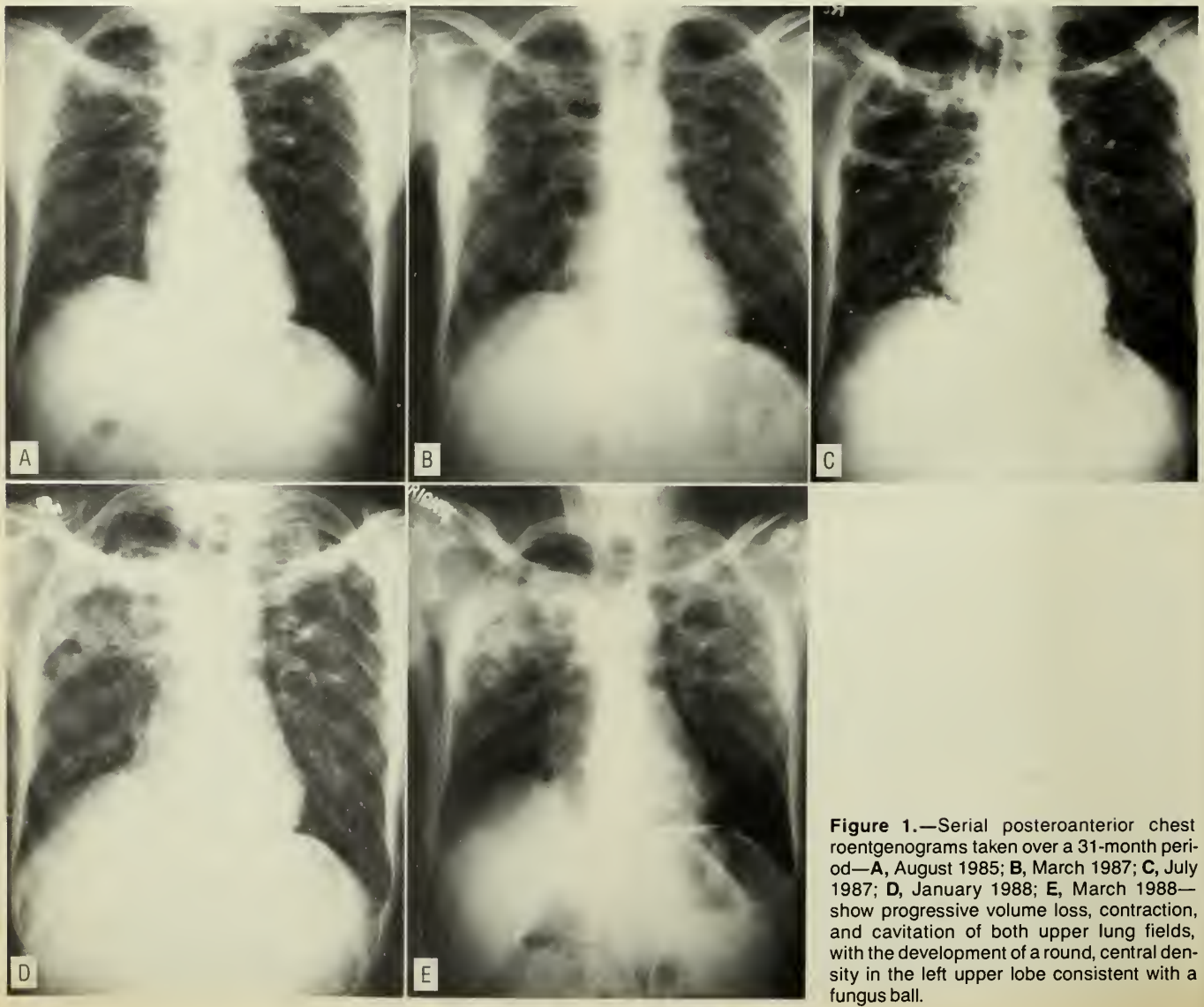



**Figure 1.**—Serial posteroanterior chest roentgenograms taken over a 31-month period—**A,** August 1985; **B,** March 1987; **C,** July 1987; **D,** January 1988; **E,** March 1988—show progressive volume loss, contraction, and cavitation of both upper lung fields, with the development of a round, central density in the left upper lobe consistent with a fungus ball.

## REFERENCES

1. Beck F: Pulmonary disease due to atypical tubercle bacilli. Am Rev Respir Dis 1959; 80:738-743

2. Corpe RF, Smith CE, Stergus I: Death due to *Mycobacterium fortuitum*. JAMA 1961; 177:262-263

3. Dross IC, Abbatiello AA, Jenney FS, et al: Pulmonary infection due to *M fortuitum*. Am Rev Respir Dis 1964; 89:923-925

4. Guest JL, Arean VM, Brenner HA: Group IV atypical mycobacterium infection occurring in association with mineral oil granuloma of the lungs. Am Rev Respir Dis 1967; 95:656-661

5. Nicholson DP, Sevier WR: *Mycobacterium fortuitum* as a pathogen. Am Rev Respir Dis 1971; 104:747-750

6. Awe RJ, Gangadharam PR, Jenkins DE: Clinical significance of *Mycobacterium fortuitum* infections in pulmonary disease. Am Rev Respir Dis 1973; 108:1230-1234

7. Chusid MJ, Parillo JE, Fauci AS: Chronic granulomatous disease: Diagnosis in a 27-year-old man with *Mycobacterium fortuitum*. JAMA 1975; 233:1295-1296

8. Dreisin RB, Scoggin C, Davidson PT: The pathogenicity of *Mycobacterium fortuitum* and *chelonei* in man: A report of seven cases. Tubercle 1976; 57:49-57

9. Wolinsky E: Nontuberculous mycobacteria and associated diseases. Am Rev Respir Dis 1979; 119:107-159

10. Varghese G, Shepherd R, Watt P, et al: Fatal infection with *Mycobacterium fortuitum* associated with oesophageal achalasia. Thorax 1988; 43:151-152

11. Gacad G, Massaro D: Pulmonary fibrosis and group IV mycobacteria infection of the lungs in ankylosing spondylitis. Am Rev Respir Dis 1974; 109:274-278

# Correspondence

## Asthma Deaths

To THE EDITOR: The concern expressed by Dr Sharma on the rising incidence of death from asthma is a real issue.[1] In his article in the November 1989 issue, the author also advocated using aerosolized corticosteroids (AC) before a trial of cromolyn sodium is attempted. I find the reasoning behind this quite puzzling. Granted that ACs are relatively safe and usually more effective than cromolyn, but they are not entirely free of side effects. Whereas ACs are not infrequently associated with oropharyngeal candidiasis and myopathy of the laryngeal muscles, cromolyn is practically free of side effects.

Even more disturbing, the author apparently overlooked the role of antiallergy management in his recommendations, even though he alluded to the fact that those who are allergic "are at an increased risk for acute severe attacks of asthma." One would reason that if allergens do play such an important role in the severe attacks, some efforts should be made to identify these allergens. As I see it, the major schism between many pulmonologists and allergists is that the former mostly neglect the roles of avoiding allergens (especially pets, house dust mites, etc) and of immunotherapy in antiasthma treatment. The rising rate of asthma deaths in the face of ever more potent antiasthma drugs would seem to highlight the fact that this battle is unlikely to be won by pharmaceutical agents alone.

JOHN T. CHIU, MD
*400 Newport Center Dr*
*Newport Beach, CA 92660*

REFERENCE

1. Sharma OP: Reducing morbidity and mortality due to asthma, *In* Epitomes—Important Advances in Clinical Medicine—Internal Medicine. West J Med 1989; 151:549

## Thymic Carcinoid and Multiple Endocrine Neoplasia

To THE EDITOR: I read with interest Venkatesh and Samaan's description of the University of Texas MD Anderson experience with six cases of thymic carcinoid tumor.[1] I am treating a similar case, and the patient is also from Texas. Because such cases are unusual and can present difficult and prolonged management problems, it may be useful to add my experience to the literature.

*Report of a Case*

A previously healthy 35-year-old man had a parathyroid adenoma resected in 1983. Chest pain subsequently developed, and a 6- by 5- by 4-cm superior mediastinal thymic carcinoid was removed during a left parasternotomy in March 1985. His serum calcium level was 2.99 mmol per liter (12.0 mg per dl), serum phosphorus 0.61 mmol per liter (1.9 mg per dl), the C-terminal parathyroid hormone (PTH) was 268.5 pmol per liter (normal 45.3 to 195.9), and the N-terminal PTH was 168.5 pmol per liter (24.2 to 66.3) at American BioScience Laboratories; a blood serotonin level was 130.4 nmol per liter (normal 283.5 to 1,134). Postoperative calcium levels remained elevated, and he received irradiation to the mediastinum. Four months later, right supraclavicular lymphadenopathy developed and was excised. Both the mediastinal tumor and the supraclavicular mass were interpreted as carcinoid, composed of small, round cells with brightly eosinophilic cytoplasm and small, round nuclei. Immunoperoxidase staining for calcitonin was negative. Notable electron-microscopic features included the presence of multiple neurosecretory granules with a dense core and halo, numerous free ribosomes, and no microvilli. The supraclavicular mass included lymph nodes and tumor extending into paralymphatic fat and connective tissue.

Both the serum calcium and PTH levels remained mildly elevated. Supraclavicular radiation therapy and fluorouracil and streptozocin chemotherapy for one year were given without change in the serum calcium or PTH values. A new right supraclavicular mass was excised in April 1986 and found to be fibrotic tissue without tumor. He was observed off therapy until recurrent pancreatitis with hypercalcemia prompted a neck exploration and the removal of a parathyroid adenoma in June 1988. The serum calcium levels returned to normal temporarily, but the pancreatitis recurred. Pulmonary nodules were discovered and removed in September 1989 and found to be recurrent carcinoid. He is now being treated with systemic infusional fluorouracil. Parathyroid hormone and serum calcium levels remain elevated, serum electrolytes are normal, and there have been no symptoms of flushing or diarrhea.

*Discussion*

Young age, an association with parathyroid tumors, male sex, prolonged survival, and the absence of the "carcinoid syndrome" are typical features seen in this and other patients with thymic carcinoid. The propensity for local and regional recurrences of the carcinoid, and our inability to definitively treat these patients with chemotherapy,[2] suggests that initial, aggressive surgical therapy, preferably through a sternal splitting incision, with complete removal of the thymus, should be carried out.

DOUGLAS W. BLAYNEY, MD
*Wilshire Oncology Medical Group*
*210 S Grand Ave, Suite 402*
*Glendora, CA 91740*

REFERENCES

1. Venkatesh S, Samaan NA: Carcinoid tumors of the thymus. West J Med 1990; 152:72-74
2. Legha SS, Valdivieso M, Nelson RS, et al: Chemotherapy for metastatic carcinoid tumors: Experiences with 32 patients and a review of the literature. Cancer Treat Rep 1977; 61:1699-1703

## Iatrogenic Illness

To THE EDITOR: I just had the opportunity to read the medical staff conference on iatrogenic illness in the November 1989 issue.[1]

The comments and observations made by Dr Tierney are all important, but I wish to point out a major omission. Call it the sixth cause of iatrogenic illness, or maybe better yet, it should be called the first or second.

The medical profession has created illness where once it did not exist. We take persons with somatic complaints for which there are no objective findings and for which there is not a true organic lesion. A good history will reveal that this class of disease is stress-induced. The physician may recog-

nize the psychogenic component for the illness but elects to disregard it and treat it as a straightforward organic illness, thereby supporting the patient's displacement of stress onto a somatic target. Since the stress is not dealt with, and since the organic illness is supported, the complaints continue and intensify over time.

There are notable examples of such illness—peptic ulcer disease is a good one. This is a stress-related disease that most physicians treat organically. Globus hystericus is another example of a disease that is invariably stress-induced and that the unsuspecting physician worsens by ordering barium swallows, esophageal manometrics, endoscopies, and follow-up appointments for the sole purpose of physical examination. More flagrant examples are the myofascial pain syndromes. Temporomandibular joint pain is an excellent example of such an illness.

The frequency of iatrogenic illness is debated. Those unskilled at diagnosis will tell you it is infrequent, if not altogether nonexistent. Those in primary care, sensitive to such problems, will tell you that 50% of what they see is stress-related, and by inference, those same patients, in the hands of someone not sensitive to psychogenic illness, will be dealing with 50% iatrogenic illness—the irony, of course, is that the illnesses are their iatrony.

TERENCE M. DAVIDSON, MD
*Professor of Surgery*
*Associate Dean for Continuing Medical Education*
*University of California, San Diego*
*225 Dickinson St (H-895)*
*San Diego, CA 92103*

REFERENCE

1. Tierney LM Jr: Iatrogenic illness (Medical Staff Conference). West J Med 1989; 151:536-541

## The War on Drugs

To THE EDITOR: What is "the war on drugs"? We think it is a fight against

- noncriminal (except that they use illegal drugs) addicts who buy the drugs;
- noncriminal nonaddicts who buy the drugs;
- organized crime (suppliers); and
- criminals who steal to continue their habit (users).

We could eliminate all but one of these adversaries—the "noncriminal" addicts—simply by decriminalizing illegal drugs. As a profession and as a society we do need to fight addiction, in the sense of helping addicts if we can. If drugs were decriminalized, we would still have that battle to wage, as we do today, but probably with not many more enemies.

Well-known political figures, such as George Schultz, are seeing the wisdom of decriminalization. The war on drugs is a war we cannot win, any more than we could win the fight against alcohol during Prohibition. If the money spent on the war against drugs were diverted to treatment for addiction, the medical profession would profit. More important, addicts and society as a whole would be a lot better off. We think it is time the medical profession took a medical and sensible stand on this subject.

Therapy Comment*
R. LAWRENCE GIBSON, MD
*14651 S Bascom Ave, Suite 225*
*Los Gatos, CA 95032*

*Therapy Comment is a group of practitioners who give consensus opinions on important professional issues.

## The Eye of the Beholder

To THE EDITOR: This is in response to the letter by Dr Arthur Vall-Spinosa in the December 1989 issue.[1]

"Glowing accounts" are somewhat in the eye of the beholder. I am very enthusiastic about a system in the United States that would permit the entire population to have access to decent medical care. Whether the Canadian health care system is the model we should emulate is open to question. There are clearly problems with the Canadian system, and transplantation to the United States might be very difficult.

Incidentally, there are not "tight limits" on the number of physicians in Canada. This was tried in British Columbia but thrown out in the courts. Certainly, the malpractice specter contributes to the cost of medicine in the United States, but it is not the major obstacle to a cost-effective national health care program.

GERARD N. BURROW, MD
*Vice Chancellor for Health Sciences*
*Dean, School of Medicine, M-002*
*University of California, San Diego*
*La Jolla, CA 92093-0602*

REFERENCE

1. Vall-Spinosa A: The Canadian system (Correspondence). West J Med 1989; 151:666

## Tryptophan Use and Fasciitis

To THE EDITOR: Tryptophan, available both through health food stores and in pharmacies as a soporific, has recently been associated with eosinophilia and myalgias.[1] We report three cases and the biopsy findings of an eosinophilic fasciitis-like process associated with inflammatory myopathy.

*Report of Cases*

The patient, a 52-year-old housewife, used 1,500 to 3,000 mg of tryptophan nightly for five years and only recently developed myalgia of her upper and lower extremities. Her creatine kinase level was normal and a complete blood count showed a total leukocyte count of $26.0 \times 10^9$ per liter with 0.45 eosinophils. A biopsy specimen of gastrocnemius muscle showed macrophages, lymphocytes, and eosinophils invading the perimysium and endomysium (Figure 1). The muscle fibers themselves appeared relatively normal, but stains for adenosine triphosphatase showed fiber type grouping.

The second patient, a 29-year-old woman, had been taking 1,500 mg of tryptophan two to three times a week to help her sleep. Progressively worsening myalgias developed, associated with a red rash and a leukocyte count of $17.6 \times 10^9$ per liter with 0.56 eosinophils. A biopsy specimen of right gastrocnemius muscle showed an inflammatory infiltrate composed of a mixture of lymphocytes, macrophages, eosinophils, and plasma cells in the fascia with spillage into the perimysium and adipose tissue. The perineurium of several nerves in the specimen showed prominent inflammatory infiltrates. Staining for adenosine triphosphatase disclosed fiber type II predominance.

The third case is most intriguing as the patient presented in 1985 with a livedo-type rash on her anterior thighs and complaints of diffuse myalgia associated with low-grade fever and 0.3 peripheral eosinophilia. A creatine kinase level was normal. She had been taking as much as 3,000 mg of tryptophan each night to help her sleep. A biopsy specimen of right gastrocnemius at that time showed a scattered in-

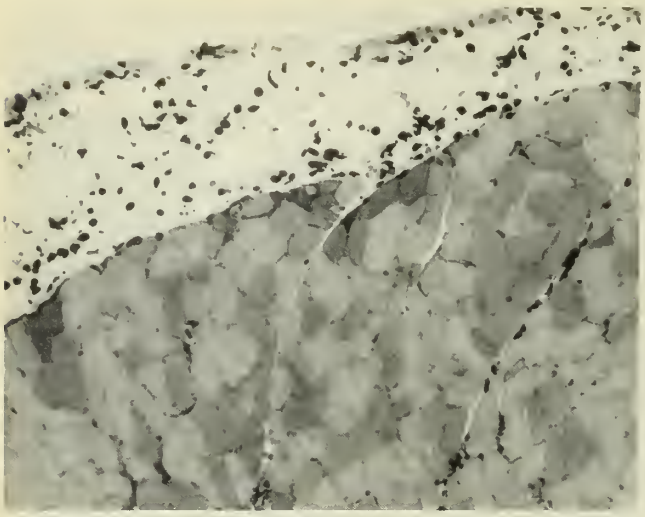


**Figure 1.**—Nonspecific esterase reaction highlights the inflammatory cells in the perimysium and endomysium (original magnification ×40).

flammatory infiltrate consisting primarily of lymphocytes and macrophages with occasional eosinophils. These cells were found in the epimysium, perimysium, and endomysium where they were particularly prominent around blood vessels and small nerves. Adenosine triphosphatase staining showed pronounced fiber type I predominance and denervation atrophy.

The pathologic examination in all three cases showed relative preservation of muscle fibers although there was a disturbance of fiber type distribution. Connective tissue within muscle fascicles as well as fascia and fat, when present, was variably infiltrated by inflammatory cells, including eosinophils. None of the biopsy specimens showed evidence of vasculitis. We noticed a propensity for the infiltrate to involve nerves and, in the second case, there was severe involvement of a muscle spindle. Nobuhiko and coworkers suggested that eosinophil-derived substances are neurotoxic and may play a role in the peripheral neuropathy associated with the hypereosinophilia syndromes.[2] A possible neuropathic component to the myalgias associated with tryptophan use warrants further investigation, particularly in light of the reported Guillain-Barré-like symptoms in some patients.[1]

Much of the clinical history and physical findings, as well as histologic features, seem indistinguishable from eosinophilic fasciitis, a disease of unknown etiology that has been reported since 1974.[3] Whether this tryptophan-associated fasciitis-like process is directly attributable to tryptophan use or is due to an unknown precipitating factor remains to be resolved. The third case raises the question of when this epidemic actually began.

BRUCE T. ADORNATO, MD
YUAN CHANG, MD
DIKRAN HOROUPIAN, MD
MAIE HERRICK, MD
ELAINE LAMBERT, MD
GEORGE V. LAWRY, MD
MARTIN STEIN, MD
*Stanford University Medical Center*
*Stanford, CA 94305-5324*

REFERENCES

1. Centers for Disease Control: Eosinophilia-myalgia syndrome and L-tryptophan-containing products—New Mexico, Minnesota, Oregon and New York, 1989. MMWR 1989; 38:785-788

2. Nobuhiko S, Furukawa S, Nishio T, et al: Neurotoxicity of human eosinophils towards peripheral nerves. J Neurol Sci 1989; 92:1-7

3. Shulman LE: Diffuse fasciitis with hypergammaglobulinemia and eosinophilia: A new syndrome? (Abstr). J Rheumatol 1974; 1(Suppl 1):46

## Integration of Prevention Efforts

To THE EDITOR: We read with interest the editorial by Dr Judson[1] that accompanied our report on efforts to control a recent outbreak of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) in California.[2] Since the purpose of our report was to only briefly describe the 1987 PPNG epidemic in southern California and make some gonorrhea-specific recommendations, we made no attempt to discuss the issues addressed by Dr Judson, especially with regard to the need to integrate traditional sexually transmitted disease (STD) and human immunodeficiency virus (HIV) prevention efforts. We agree, however, that this is an important issue, and we would take this opportunity to comment on how the California Department of Health Services (CDHS) has tried to integrate STD and HIV prevention efforts.

The need to integrate traditional sexually transmitted disease prevention efforts (along with drug abuse prevention and treatment and various other activities) with HIV prevention efforts has long been recognized by the CDHS. We have repeatedly made this point in the past several years at many medical and non-medical forums. Indeed, this point was stressed in our response to the California legislature during its consideration a few years ago of creating a separate state department of AIDS (acquired immunodeficiency syndrome). We have strongly resisted efforts such as this because of our belief that there is a critical need to integrate HIV disease prevention efforts with numerous other public health and publicly funded health care programs.

Our specific efforts to integrate HIV and other STD prevention efforts include the following:

- All of our STD intervention staff have been trained in HIV pre- and post-test counseling techniques, and they integrate risk assessment and behavior messages into the STD interview process.
- Confidential HIV antibody testing is offered, along with routine pretest counseling, to every STD clinic patient. Assistance in notification of sex or needle-sharing partners, or both, is provided to patients with positive test results.
- Program managers for STD regularly influence HIV-related policy through a long-standing interagency AIDS planning committee, as well as through other intradepartmental processes.
- Traditional STD and HIV prevention efforts have been combined to conduct knowledge, attitudes, beliefs, and behaviors surveys in STD clinics and to strengthen outreach activities to high risk groups through demonstration projects with community-based organizations. Current projects involve STD and HIV screening targeted to inner-city pregnant women, many of whom are addicted to crack cocaine. Other projects offer testing for infectious diseases common to addicts seen at drug rehabilitation centers.
- Sexually transmitted disease and HIV disease are jointly targeted in California's public information campaigns, and both programs have helped formulate health education criteria in the public school system.

Despite the fact that policy and funding decisions by state and federal elected officials have forced the separation of HIV disease and other STD prevention programs, multiple

efforts to integrate these programs have been made in California. And while not as fully integrated as we would like, it has been our long-standing and often stated position that administrative separation of HIV prevention efforts from other STD control efforts is artificial and, we hope, temporary.

KENNETH W. KIZER, MD, MPH
JAMES A. FELTEN, MPA
VAUGHN A. JODAR
HIROSHI E. YAMAMOTO
JEAN M. MONTES
*California Department of Health Services*
*714 P St, Rm 1253*
*Sacramento, CA 95814*

REFERENCES

1. Judson FN: Controlling penicillinase-producing *Neisseria gonorrhoeae*—Does it really matter anymore? (Editorial). West J Med 1989; 151:319-321

2. Kizer KW, Felten JA, Jodar VA, et al: Penicillin-producing *Neisseria gonorrhoeae* in California—Report of a major outbreak and control recommendations. West J Med 1989; 151:292-295

## Life-style and Illness

To THE EDITOR: I would like to respond to your editorial in the January 1990 issue entitled, "Health Care—Where Are the Problems and Where Are the Solutions?"[1] The problem is people. In your editorial, you state "The problems are actually the problems of illness rather than of health, and the first and most important steps in health care have to be taken where the sick, injured, or emotionally disturbed person is, with the resources for care that are available. This is what health care is all about. Yet there are many who view it differently. They see it more as a national problem that, therefore, requires a national solution by which they mean a nationalized system for rendering patient care. This view is reinforced by the rising cost of health care which is now nationwide, and has become a problem not only for the person afflicted, their families, and the immediate community, but for business and industry and even for government at the local, state, and national levels." You note also, "there is a notable tendency to push responsibility for paying the cost downward. It could be that the present day problems of health care can be better solved from the bottom up. . . Americans are pretty good at solving their problems when they recognize a need."

There are some of us who view the health care problem differently. We do indeed see it as a national problem that requires a national solution. That national solution is not a national health care payment plan, however. What I see is the need for a national program on governmental, both federal, state, county, and private sector, programs in educating people to make appropriate life-style and dietary choices and reduce most of the illnesses that now afflict us.

Currently, we are spending around 97% to 98% of our health care dollars in diagnosing and treating established disease. We are spending a pittance in trying to educate people to avoid those diseases.

What if the California Medical Association and the American Medical Association would take the lead in spending some time and money to produce public education spots for radio, television, and the print media promoting good health and counteracting much of the pernicious advertising that is destructive to our health? I think we could do a great deal to improve the image of medicine by taking a positive prohealth stand in the media.

The solutions to most of our health care problems are amazingly simple. The problem is getting people to make appropriate choices in their life-style and dietary practices. To accomplish this, we must educate our patients. As organized medicine, let us take a pro-health stance and not just wait to pick up the pieces when the machine falls apart.

IRA E. BAILIE, MD
*1015 E Main St*
*Turlock, CA 95380*

REFERENCE

1. Watts MSM: Health care—Where are the problems and where are the solutions? (Editorial). West J Med 1990; 152:68-69

# Topics in Primary Care Medicine

## Dupuytren's Disease

STEVEN M. GONZALEZ, MD, *Caldwell, Idaho, and* RICHARD I. GONZALEZ, MD, *Woodside, California*

*"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.*

STEPHEN J. McPHEE, MD
TERRIE MENDELSON, MD
Series' Editors

Dupuytren's disease is a fibrotic thickening of the palmar fascia initially manifested as painless nodules of one or both hands and subsequently by permanent contractures of one or more fingers into the palm. Every primary care physician sees Dupuytren's disease because it is the most common affliction of the hand, affecting 25% of persons of Celtic ancestry and as many as 5% of the general population. Interesting associations with other localized fibrotic disorders such as knuckle pads (Garrod's nodules), Peyronie's disease, and plantar fibrosis (Ledderhose's disease) have been recognized. Primary care physicians should be prepared to recognize the various stages of the disease and to make an appropriate referral before disabling and often irreversible contracture occurs.

Since Baron Guillaume Dupuytren's description of a peculiar retraction of the fingers into the palm in 1831, the disease that bears his name has come under intense scrutiny and yet remains an enigma. First noted by Plater in 1680, referred to in lectures by Henry Cline in 1808, and related to hypertrophy of the palmar fascia by Sir Astley Cooper in 1822, the strange affliction was popularized by Dupuytren in 1831 in his classic account of permanent retraction of the fingers in the first chapter of his work, *Leçons Orales de clinique chirurgicale faites a l'Hotel-Dieu de Paris.* Dupuytren described the first known surgical correction, which entailed making transverse incisions through the palmar aponeurosis and through the contracture at the proximal interphalangeal joints. After two months of splinting, the patient regained normal function. In the same work, Dupuytren gave a description of symptoms and findings that is still useful. He further stated that the palmar aponeurosis was the cause of the retraction, discounted influences of the tendons and skin, and hypothesized a traumatic etiology.

Slightly more than a year later, Dr G. Gayrand at the Hotel-Dieu at Aix presented new findings to the medical academy in Paris in April of 1834. He noted that the skin and subcutaneous tissues were actively involved but with little involvement of the palmar aponeurosis, and with fibrous cords passing from the aponeurosis to the flexor tendon sheaths. He questioned a traumatic cause, noting bilateral involvement in a patient who had not performed manual labor. Finally, he questioned Dupuytren's technique, calling for a longitudinal incision with excision of the contractile band. Currently the controversy has been carried into the courts as members of the legal profession now debate the same issues to determine financial compensation to workers of various occupations so afflicted.

### Anatomy

The palmar fascia is composed of a superficial and deep layer, with anchoring fibers passing to the palmar skin superficially and to the interosseous fascia deeply (Figure 1). The superficial palmar fascia (of the palmar aponeurosis) is a broad, triangular sheet with its apex at the wrist and its distal portions dividing into longitudinal slips as it passes toward the fingers. Most of the distal fibers pass upward to the skin, forming a strong attachment between the palmar fascia and the skin, most prominently at the distal palmar crease. Other fibers run transversely to form the interdigital ligaments of the finger webs or deeply to join or interdigitate with fibers ascending into the finger. The deep palmar fascia is predominantly transverse and thickened centrally, passing from the transverse carpal ligament to the four central digits. Passing downward from the deep fascia are fibrous slips that form eight tunnels for the lumbricals and the flexor tendons of the four central fingers. Thus, the palmar fascia fixes the skin during gripping and twisting maneuvers, impedes hyperextension of the fingers, and provides functional stability to the flexor mechanism. Dupuytren's disease variably involves portions of the entire apparatus.

### Histology

The lesions of Dupuytren's disease resemble normal scar tissue with fibroblastic proliferation and collagen accumulation. The nodules are more cellular than the longitudinal bands, with numerous fibrocytes arranged in a concentric pattern. The bands are devoid of cells and are composed of wide sheaths of collagen fibers. The most histologically active lesion appears to be the subcutaneous nodule, which is probably the initiating site. Fibrosis may extend to the

(Gonzalez SM, Gonzalez RI: Dupuytren's disease. West J Med 1990 Apr; 152:430-433)

From the Department of Surgery, Stanford University School of Medicine, Stanford, California. Dr Steven Gonzalez is currently in private practice in Caldwell, Idaho.

Reprint requests to Steven M. Gonzalez, MD, 222 E Elm, Caldwell, ID 83605.

dermis, accounting for the skin contractures and dimples. The histologic appearance of the knuckle pads and the plantar nodules is similar.

Three histologic phases occur in sequence, much as in the formation of normal granulation tissue. The early proliferative phase is characterized by fibroblastic proliferation. The appearance of myofibroblasts and type III collagen marks the involutional phase, and the residual phase is marked by the appearance of fibrocytes and type I collagen until an acellular dense band is formed. The presence of myofibroblasts in nodules or fibroblasts with microtubular structures in the fascia of resected specimens is predictive of recurrence. Increased numbers of myofibroblasts and type III collagen can also be found in grossly normal aponeurotic tissue in Dupuytren's disease, serving as sites for postoperative recurrences.

## Etiology

The initiating event that propagates the cascade of fibrosis remains unknown. Since Dupuytren's time, the relative contribution of trauma or microtrauma has been debated. Dupuytren's disease is not related to occupation, nor is it more prevalent in those performing manual labor. It involves the nondominant as often as the dominant hand and the ulnar rather than the radial aspect. No suitable explanation has been given for the often-noted association with alcoholism, epilepsy, or diabetes mellitus. Specific hormone receptors have not been found in the fibrotic band, nor has research uncovered the nature of the predisposition in men. A dominant hereditary pattern appears to be present in those of Celtic ancestry. A positive family history is reported by 25% of unselected patients, with large kindred investigations finding aspects of the disease in 68% of first-degree relatives of affected patients, suggesting an autosomal-dominant pattern of inheritance. Antibody to denatured type II collagen is found more commonly in those of the HLA-DR4 genotype. Thus, there appears to be a genetic predisposition that sensitizes a person to form a contracture after a yet-unknown stimulus.

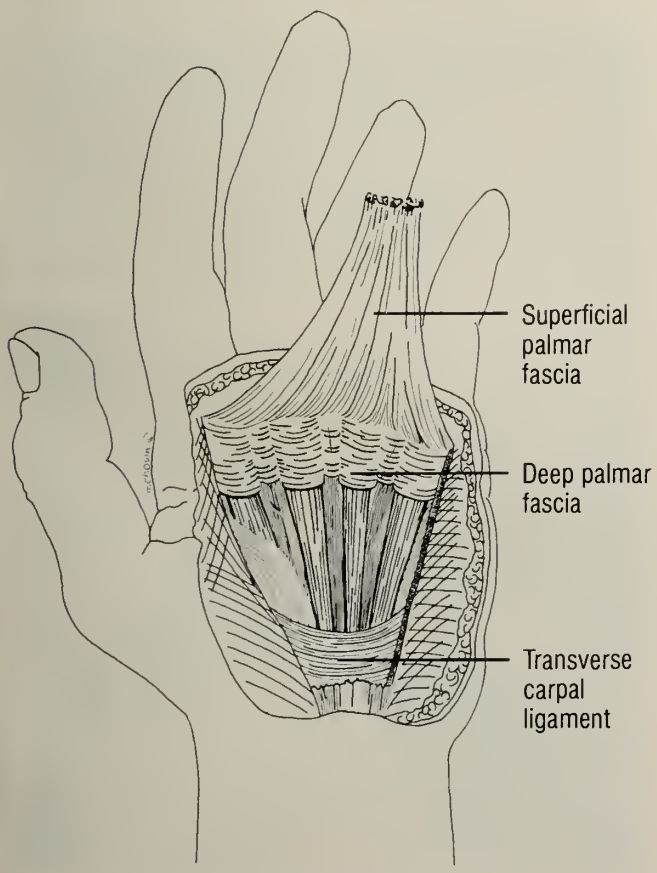



**Figure 1.**—The deep transverse and superficial longitudinal palmar fasciae are depicted. Note the tunnels formed for the passage of the lumbricals and flexor tendons. Dupuytren's disease involves components of the entire apparatus.

## Incidence

The prevalence of Dupuytren's disease is greatly influenced by the population studied. It is found almost exclusively in persons of Celtic ancestry. Its geographic distribution reflects patterns of Celtic migration during the 5th century to Britain and western Europe. Subsequent selective immigration to Australia and the eastern coast of North America accounts for the high prevalence rates in these areas. Dupuytren's disease is extremely uncommon in persons of African or Asian descent. It is present in 4% to 5% of unselected populations, but in Melbourne, for example, the disease affects 20% of the population aged 60 and older and 40% of those aged 80 and older. In the British Isles, 25% of men older than 65 are so afflicted, and in France Dupuytren's disease was found in 12% of nonalcoholic patients averaging 54 years of age. Men are affected twice as often as women before age 40, but the difference lessens thereafter, although in men the disease more commonly progresses to flexion deformities. The disease is rare before age 25, typically occurring after age 40.

Associations with epilepsy, alcoholism, diabetes mellitus, and chronic pulmonary tuberculosis have been noted, although no association with epilepsy was reported until after the introduction of anticonvulsants in 1940. Hueston cites a 43% incidence in men with epilepsy younger than 40 years, a 44% incidence in alcoholic patients, and a 42% incidence in patients with chronic pulmonary tuberculosis. Prospective studies using univariate and logistic regression methods on patients admitted to hospitals have shown a significant relationship between age, total alcohol consumption, and Dupuytren's disease, with the severity of disease related only to the amount of alcohol consumed. No relationship to chronic liver disease or manual labor was noted.

## Clinical Aspects

Dupuytren's disease is usually bilateral (65%) but often not symmetric. The palm is involved in almost all cases (95%), with the ring or small finger involved in as many as 75% of patients. The middle finger is affected in as many as 75% of patients. The index finger is involved least frequently (13%), and the thumb and long fingers are affected in about a third of cases.

At first a small painless nodule may appear at the distal palmar crease opposite the affected finger. The skin generally becomes fixed to the underlying fascia with a characteristic dimpling. This usually presents no more than an inconvenience to the patient and is easily ignored. Pain at this stage should suggest another cause. The fibrotic process may not progress further, as is often the case in women, or may begin to cause flexion contractures at the metacarpophalangeal joint of the ring and subsequently the adjoining fingers. Later the proximal interphalangeal joint may become affected as well.

The transition from palmar nodules to flexion contracture may occur rapidly over the space of a year or more slowly over as long as two decades. The proximal interphalangeal joint may then become involved, flexing the finger into the palm and completely inhibiting normal grip. The hooklike contracture may predispose to injuries because the contracted fingers catch on machinery or rails (Figure 2). The skin macerates and becomes secondarily infected at the level of the flexion creases or interdigitally.

The association of Dupuytren's disease with knuckle pads, plantar fibrotic nodules, and Peyronie's disease has been called the "Dupuytren's diathesis." Of patients so affected, 44% show tender nodules over the dorsum of the proximal interphalangeal joints, preventing the wearing of rings. The nodules (Garrod's knuckle pads) appear earlier than the palmar nodules and often regress as the other manifestations of the disease progress. Plantar nodules are seen in 18% of patients, although they also occur at an earlier age and can become large and painful. Histologically they can be confused with fibrosarcoma, leading occasionally to inappropriate amputation. The nodules usually regress spontaneously, often followed by further recurrences. Attempted surgical removal usually leads to additional disability. In 3% of patients with Dupuytren's disease, signs of Peyronie's disease will develop. Peyronie's disease is a fibrotic disorder of the penile shaft leading to anterior angulation. A familial transmission of Peyronie's disease has been reported, with 78% of affected persons also having Dupuytren's disease. The use of $\beta$-adrenergic blockers has been associated with Peyronie's disease, although no such association has been found in Dupuytren's disease. The Dupuytren's diathesis also includes shoulder stiffness, fascial fibromatosis, a loss of joint mobility, a loss of thoracic and lumbar spine motion, and diffuse fibrosis of the shoulder, hip, anterior leg, or antecubital space.

The diagnosis is usually straightforward when physicians are presented with a thickened palmar aponeurosis and associated finger contracture. Occasionally, however, other conditions mimic the contractures caused by Dupuytren's disease (Table 1). Traumatic linear midline scars can cause

TABLE 1.—*Differential Diagnosis of Dupuytren's Disease*

| *Differential Diagnosis* | *Differentiating Factor* |
|---|---|
| Congenital flexion deformity | Appropriate history |
| Posttraumatic scar | History of trauma or burn |
| Flexion contraction due to immobilization | Appropriate history |
| Volkmann's ischemic contracture | Wrist and PIP joint flexed |
| Primary joint contracture | Palm unaffected, painful joint, associated systemic disease evident, history of trauma |
| Postinflammatory flexor tendon contraction | Trigger finger |
| Fibrosarcoma of the palm | Does not progress to contracture, painful |
| Plantar fasciitis | Associated with painful arthritis and systemic malignancy |

PIP = proximal interphalangeal

TABLE 2.—*Poor Prognostic Factors in Dupuytren's Disease*

Positive family history
Male sex
Associated alcoholism or epilepsy
Bilateral involvement
Associated knuckle pads or plantar nodules
Aggressive behavior of the contraction

**Figure 2.**—Dupuytren's disease is shown involving the ring finger. Note the thick contractile band, skin dimpling, and the hooklike contracture that predisposes to an accidental attachment to machinery and railings.

**Figure 3.**—Dupuytren's disease is shown involving the middle finger. Note the slight contracture of the proximal interphalangeal joint—an indication for immediate surgical correction.

contractures of the digital joints. In contrast to the contractures of Dupuytren's disease, in which the contracting band is dermal or subcutaneous, linear traumatic scars are limited to the superficial layers of skin. Joint contractures after trauma or arthritis can be differentiated by history and x-ray films. Although a damaged flexor tendon may result in a flexion deformity, there is no palpable subcutaneous band. A "dropped finger" of an extensor tendon injury can be corrected passively, whereas a contracted finger in Dupuytren's disease is fixed. A long-standing trigger-finger deformity can cause locking of the digit, but the locked tendon can be released by sharply flexing the finger at the middle interphalangeal joint while passively extending the digit. Knuckle pads and plantar nodules should alert the physician to the presence of Dupuytren's disease as well.

## Prognosis

Milford has defined six factors that indicate a poor prognosis (Table 2). Contractures involving the central longitudinal pretendinous band respond well to surgical treatment. Involvement of the deep transverse intermetacarpal ligament, however, with its attachment to the joint capsule or the proximal interphalangeal joint and the associated entrapment of the digital nerve, makes repair hazardous and often ineffective. Contractures of the metacarpophalangeal joints are more easily repaired than are those of the proximal interphalangeal joints, with the latter often impossible to repair in neglected cases.

## Treatment

No satisfactory treatment yet exists for Dupuytren's disease. Nonsurgical treatments such as local corticosteroid injections, ultrasound, topical ointments, and vitamins have been tried without success. The traditional method of sitting on one's hands, palmar side down, is probably as effective as most treatments in the early stages. Treatment strategies must be tempered by the extreme variability of disease presentation and the rate of progression. Several points are noteworthy, however. Simple nodular disease of the palm need not be approached surgically. Patients with nodules may have no further progression and may remain asymptomatic indefinitely. Minimal flexion contractures of the metacarpophalangeal joints can be stable and nondisabling and can be repaired successfully later. Even minimal involvement of the proximal interphalangeal joint should be surgically repaired immediately (Figure 3) because permanent contracture not amenable to later surgical repair is likely to occur. In all cases, cautious observation is recommended with careful instructions to patients to return immediately if any interphalangeal involvement develops.

The choice of surgical therapy depends greatly on the degree of involvement, a patient's age and general physical status, and whether the operation is being done for a recurrence. Each approach necessitates considerable surgical skill and experience. In an elderly or infirm patient, a limited subcutaneous fasciectomy can be done that is palliative, but it is associated with a 72% recurrence rate. A partial selective fasciectomy suffices when only one or two ulnar fingers are involved. This limited operation is associated with a low complication rate, and, although recurrence is again frequent, only 15% need another operation. Both diseased and grossly normal palmar fasciae are removed by complete (radical) fasciectomy. This operation has generally been abandoned because of an unacceptable complication rate. Occasionally a limited fasciectomy can be combined with an extensive fasciectomy of any involved finger. Fasciectomy with skin grafting offers an excellent choice for a patient with a poor prognosis or in those with recurrence. The complication rate is low, and the procedure offers the lowest recurrence rate.

Complication rates generally reflect the skill and experience of the surgeon and include hematoma, skin necrosis, infection, digital nerve transection, sympathetic dystrophy, and recurrence. Only occasionally is a digit lost from a surgical mishap. Recurrence rates continue to be about 20%, reflecting the continued progression of the fibrotic process despite temporary surgical correction.

## Summary

Dupuytren's disease is an extremely common malady, affecting as many as 3% of the general population. Presenting features are variable and include simple asymptomatic palmar nodules or refractory contractures of the interphalangeal joints. Substantial associations with knuckle pads, plantar nodules, and Peyronie's disease are noteworthy. Although a strong familial tendency is present, the precise pathologic mechanism is unknown. Treatment is frequently unnecessary, but when indicated it includes a variety of surgical alternatives. An appropriately timed referral to a surgical specialist before irreversible contracture of the interphalangeal joints can prevent a permanent loss of function. When surgical intervention is not elected, careful and regular follow-up is necessary to detect early joint contracture.

### GENERAL REFERENCES

Attali P, Ink O, Pelletier G, et al: Dupuytren's contracture, alcohol consumption and chronic liver disease. Arch Intern Med 1987; 147:1065-1067

Gelberman RH, Amiel D, Rudolph RM, et al: Dupuytren's contracture—An electron microscopic, biochemical and clinical correlative study. J Bone Joint Surg (Am) 1980; 62-A: 425-432

Hueston JT: Dupuytren's Contracture. Edinburgh and London, E&S Livingstone, 1963

Hueston JT, Tubiana R: Dupuytren's Disease. New York, Grune & Stratton, 1974

McFarlane RM: Dupuytren's contracture, chap 12, *In* Green DP (Ed): Operative Hand Surgery—Vol 1, 2nd Ed. Edinburgh, Churchill Livingstone, 1988, pp 553-589

McFarlane RM: Dupuytren's disease, chap 23, *In* Unsatisfactory Results in Hand Surgery. Edinburgh, Churchill Livingstone, 1987, pp 348-364

Milford L: Dupuytren's contracture, chap 13, *In* The Hand. St Louis, CV Mosby, 1982, pp 276-281

Viljanto JA: Dupuytren's contracture: A review. Semin Arthritis Rheum 1973; 3:155-176

# Health Care Delivery

## Health Care Needs and Services for Technology-Dependent Children in Developmental Centers

LUCY S. CRAIN, MD, MPH; DONALD N. MANGRAVITE, MD, MPH; ROBERT ALLPORT, MD; MARIANNE SCHOUR, MD, MPH; *and* KRIST BIAKANJA, MD, *San Francisco*

*In an attempt to document the trend toward a more seriously ill and medically needy population of children in California state developmental centers, we studied the medical status and health care needs of the pediatric and young adult population (birth to 22 years of age) residing in all acute care and skilled nursing care units in developmental centers in 1988. All children in California's state developmental centers are severely to profoundly mentally retarded and chronically disabled, and many have serious health problems. Of the 865 children in 5 developmental centers, 441 (51%) resided in acute and skilled nursing care units and were technology dependent (Office of Technology Assessment classification). We suspect that our findings (ethical and quality-of-care issues, staffing, licensing mandates, cost-of-care considerations) reflect the rapidly expanding population of children with special health care needs and may be important in planning for services in other states as well as in California.*

(Crain LS, Mangravite DN, Allport R, et al: Health care needs and services for technology-dependent children in developmental centers. West J Med 1990 Apr; 152:434-438)

In 1978 the Committee on Children with Disabilities of the Northern California Chapter I of the American Academy of Pediatrics published a report titled "Medical and Health Care in State Residential Institutions for Children and Youths."[1] Much has changed in state hospital systems in California and other states in the past decade, and this 1988 study by the Committee on Children with Disabilities documents some important trends in the changing residential population and in the increasing complexity of health care needs and services required by that population. Because children with special health care needs make up an increasing percentage of the pediatric population in these residential institutions, we found it necessary to describe these most medically needy children in California developmental centers to better define their health care needs, to describe changes or trends or both in this population, and to assist the California State Department of Developmental Services (DDS) in planning how to appropriately serve this population in the future.

California's former state hospitals are now designated state developmental centers, and the term "resident" or "client" is used instead of "patient." Today's terminology reflects the general attempt to abandon the medical model of services for persons with developmental disabilities, an effort that appears ironic in view of the health care needs of the current residential population. This is more than a semantic exercise: since 1982, California's DDS has not required accreditation of the state developmental centers by the Joint Commission on Accreditation of Hospitals.[2] The centers are now accredited by the Accreditation Council for Persons With Developmental Disabilities,[3] an educational-functional abilities program accreditation model. The state's Department of Licensing and California's Medi-Cal (title XIX), however, have specific minimum staffing ratios and other standards that are met by the surveyed centers.

As community educational programs and other resources for persons with developmental disabilities have expanded in the past decade, the population of children and youths with such disabilities (birth to 22 years of age) in all California state developmental centers has fallen from a high average monthly census of 3,968 in 1976 to a current low of 1,099. Since 1980, only children with developmental disabilities requiring skilled nursing care and for whom no care alternative existed have been admitted to California state developmental centers, and the number of young children requiring such admission has not increased significantly in recent years. The health care needs of those now admitted are much more complex, however, and their health status is more fragile than that of children who can be cared for in less restrictive environments. Despite increasing numbers of technology-dependent infants and children, some of whom have developmental disabilities, there has been no concomitant increase in community facilities capable of caring for those children for whom care is unavailable either at home or in an acute care hospital. Many young children are admitted directly from a pediatric intensive care unit to a state developmental center, and some remain in acute care hospitals for weeks while community care alternatives are sought. Increasing emphasis on the need for creating community alternatives for persons with developmental disabilities produced a sense of urgency to describe health care needs and services for medically fragile and technology-dependent residents of the California developmental centers, recognizing that these

From the Department of Pediatrics, University of California, San Francisco, School of Medicine, and the Committee on Children with Disabilities, Chapter 1, District IX, American Academy of Pediatrics.

Reprint requests to Lucy S. Crain, MD, MPH, UCSF Medical Center, Box 0314, 400 Parnassus, Rm A206, San Francisco, CA 94143.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CPR = cardiopulmonary resuscitation
DDS = Department of Developmental Services
DNR = do-not-resuscitate [orders]
HIV = human immunodeficiency virus
OTA = Office of Technology Assessment

children are an identifiable minority of technology-dependent children in California. (Most technology-dependent children already reside in the community, usually in their family's home.)

## Patients and Methods

Using the Office of Technology Assessment (OTA) definition of a technology-dependent child as one from birth through 21 years of age having a chronic disability, who needs "both a medical device to compensate for the loss of a vital body function and substantial and ongoing nursing care to avert death or further disability,"[4] we restricted our study to the subpopulation of 441 children residing in skilled or acute nursing care programs in California state developmental centers. The 424 children and youths residing in other state developmental center programs—that is, those for social development, sensory development, behavior adjustment, and habilitation—were described by the DDS as not having special health care or skilled nursing care needs and were not included in our data analyses. We also excluded from this study about 500 children and youths with emotional disorders who reside at other state developmental centers and are described as not having special health care needs.

At each institution, we scheduled a single meeting during fall 1987 and discussed study goals and data collection with the center administrator, medical director, nursing administrator, and medical and nursing staff. After this meeting, medical and administrative staff gave members of our study subcommittee tours of all programs and units providing care for medically fragile and technology-dependent children and youths.

Two study guides were developed to provide systematic instruments for data gathering. The first guide included questions regarding total and age-specific census; physician and service resources; routine dental protocol, education, therapy, and equipment; and general trends over the past decade. The second guide was a patient profile that described each client's characteristics in detail—birth date, date of admission, diagnosis and cause of disability, specific nursing care requirements, equipment needs, state of responsiveness, and medications. These profiles were completed by development center staff for each client and were coded to ensure confidentiality. All data were reviewed and tabulated by our subcommittee during the winter and spring of 1987-1988. Each client was then listed according to the OTA categories for technology dependence (Tables 1 and 2).[4]

## Findings

The State DDS operates seven developmental centers; however, skilled or acute levels (title XXII licensing regulations) of nursing care for persons younger than 22 years are available only at the five surveyed centers (two of which are in northern California, two in southern California, and one in central California). Although we found the distinction between acute and skilled nursing care needs difficult to determine for many of these children, such licensing designations are essential in determining both staffing ratios and the rates of Medi-Cal (the state's medicaid system) reimbursement. Only two developmental centers (one in southern and one in central California) are physically equipped to provide assisted ventilation services. We found variations in service capabilities to be dependent on the availability of equipment, trained personnel in the surrounding communities, budgetary constraints, and differences in physical plants at the institutions.

### *Patient Profiles*

Of the 5,773 clients (aged 4 months to 94 years) residing in the five surveyed developmental centers, 865 (15%) were younger than 22 years. Of these 865 persons, 441 (51%) children and youths were technology-dependent patients (Table 1). The percentages of technology-dependent children at each center ranged from 41% to 63.6%.

All 441 children were dependent on one or more medical devices, and all required skilled nursing care. There were 11 ventilator-dependent persons (OTA group I). None required parenteral alimentation or prolonged intravenous administration (OTA group II), although several children in acute care units were receiving short-term intravenous fluid or medications. While all ventilator-dependent children resided in acute care units, those with tracheostomies or who were dependent on other devices resided on skilled nursing units unless acutely ill. Group III includes children who depend

TABLE 1.—*Technology-Dependent and Total Resident Census at the State Developmental Centers*

| Institution | Total Census | Developmentally Disabled Children and Youths, Ages 0 to 22, Census No. | Technology-Dependent Children, Number | Technology-Dependent Children, Percent |
|---|---|---|---|---|
| A | 1,100 | 170 | 72 | 42.4 |
| B | 1,375 | 187 | 119 | 63.6 |
| C | 1,164 | 129 | 53 | 41.1 |
| D | 1,084 | 216 | 94 | 43.5 |
| E | 1,050 | 163 | 103 | 63.2 |
| Total | 5,773 | 865 | 441 | 50.9 |

TABLE 2.—*Office of Technology Assessment Technology-Dependent Groups at Institutions Surveyed (Ages 0 to 22 Years)*

| | Institution A | B | C | D | E | Total |
|---|---|---|---|---|---|---|
| Group I | | | | | | |
| Ventilator-dependent | 0 | 0 | 7 | 4 | 0 | 11 |
| Group II | | | | | | |
| Prolonged intravenous drugs or nutrition | 0 | 0 | 0 | 0 | 0 | 0 |
| Group III | | | | | | |
| Gastrostomy | 31 | 78 | 36 | 89 | 57 | 291 |
| Nasogastric or orogastric tube | 17 | 1 | 4 | 0 | 4 | 26 |
| Tracheostomy | 15 | 9 | 14 | 58 | 19 | 115 |
| Oxygen support | 0 | 0 | 1 | 53 | 2 | 56 |
| Group IV | | | | | | |
| Cardiorespiratory monitors | 0 | 2 | 11 | 14 | 13 | 40 |
| Substantial nursing care | 72 | 119 | 53 | 94 | 103 | 441* |

*Total of above columns exceeds 441 because many clients are dependent on 2 or more technologic interventions. All require substantial nursing care.

daily on other respiratory or nutritional support, tracheostomy care, suctioning, oxygen support, or tube feeding. These make up the majority of the technology-dependent children and youths in California developmental centers. There were 115 children with tracheostomies, and 56 required oxygen. Feeding gastrostomies were the most common technology-dependent devices, required by 291 (66%) of the total 441 children (Table 2). An additional 26 required nasogastric or orogastric feeding tubes for nutritional support. Several children (258) were dependent on two or more technologic devices. Children in OTA group IV required specialized nursing care at a lesser level of acuity than did the first three groups and included 40 children needing electronic monitoring, several of whom also had urinary catheters, colostomies, or jejunostomies. Although these children were not actually dependent on technologic devices to support or maintain life, their associated disabilities necessitated substantial nursing care.

*Etiology*

Near drowning was second only to perinatal hypoxia (59 and 82 patients, respectively) as the most common associated etiologic event. Accidental drowning in the ocean, swimming pools, lakes, and rivers has long been acknowledged as a leading cause of death of young children in California, but 15% of this study's severely disabled children had almost drowned in bathtubs or basins. Histories of vigorous and prolonged resuscitation were evident for all 59, regardless of the circumstances of the drowning incident. Several young children had severe disabilities associated with the congenital rubella syndrome, and several children at each institution were identified as victims of child abuse. Among other possibly preventable disabilities were unshunted massive hydrocephalus in 25 children and postnatal anoxia in 14—including accidental suffocation, perisurgical anoxia, and attempted suicide.

*Nursing and Physician-to-Patient (Client) Staffing Patterns*

The nurse-to-patient ratio on acute care units was 1:4 to 1:6 (varying with shifts) and on skilled nursing facility units from 1:6 to 1:12. Physician-to-patient ratios on acute care units varied from 1:13 to 1:66, the latter unit including both adults and children and seven children who were ventilator-dependent. (This contrasts with a local community pediatric intensive care unit caring for children with similar technology-dependent needs, which has 1:2 nurse-to-patient and 1:4 physician-to-patient ratios.) With few exceptions, the general quality of medical and nursing care was excellent. Pediatricians now constitute about 20% of the physicians at the developmental centers, in contrast to their 7.7% component in 1978—a direct result of action by the DDS on the 1978 American Academy of Pediatrics recommendations for increased pediatric staffing to improve the quality of health care for children in state hospitals. All acute care units surveyed were staffed by one or more board-eligible or board-certified pediatricians.

*Trends*

In 1978 there were 3,500 children residing in all California state hospital developmental disabilities programs, 22% of the total residential developmental disabilities population. Today's total census of 1,099 children and young adults (from birth to 22 years of age) represents 16% of the total 6,817 resident population and is reflected by an increased mean age of the state developmental center residents (mean ages of 12 years in 1978 and 30 years in 1988).

All developmental centers continue to be major economic entities and employers in their locales. As society has progressed toward providing more opportunities for "normalization" of persons with disabilities, such efforts have also become evident within the institutional context. The client population of developmental centers has become much more visible in the local communities. Several children from skilled nursing and other units at each developmental center are transported daily by school bus to local special education classes in nearby community public schools. All but the most medically unstable residents of the centers enjoy regular field trips as part of educational and activity programs, including trips to the zoo, to recreational, music, and sports activities, and to participate in the Special Olympics. A positive interaction with local communities is the recruitment and training of "foster grandparents" by the centers—that is, usually retirees in the local community who, after training, come to visit, hold, and help care for their assigned "grandchild" on a regular basis. Fewer than half of the children's biologic families maintain direct contact with their child in the skilled nursing programs. Although the centers welcome and encourage such ongoing involvement, staff reported that family contact is often precluded by parental death or by the choice of families who describe ongoing contact with their severely disabled child as "too painful."

*Severity or intensity of health care needs.* No children requiring ventilators, suctioning, tracheostomies, or oxygen (OTA groups I, II, and III) resided in the skilled nursing units in 1978, and fewer than 30 children in the acute care units in our earlier study had gastrostomies or required tube feeding. The first ventilator-dependent child was admitted to a California developmental center in 1983. The 441 technology-dependent children (244 of whom were described as being in a chronically vegetative state) identified in this study constitute a new population who did not reside in state hospitals ten years ago.

*Costs of care.* In 1978 state hospital costs for children and youths ranged from $60 to $150 per day ($108 to $271 in June 1988 dollars) (US Department of Labor, "The Purchasing Power of the Dollar," written communication, June 1988). Costs of care in acute medical or surgical units at the five surveyed developmental centers in 1988 ranged from $189.31 per day ($69,098 per year) to $558.46 per day ($203,837.90). The average cost of care (including all aspects of the resident's program services) for a ventilator-dependent child was $200,000 per year. Costs of care on continuing medical care units ranged from $156 to $210 per day. On treatment and social development units (more comparable with the levels of care provided in the 1978 study programs), costs were $144 to $190 per day. Costs of care are largely determined by staffing levels. We compared staffing patterns on acute care and skilled nursing units with local community hospital pediatric intensive care nurseries where the cost of care ranged from $995 to $1,093 per day for ventilator-dependent babies and from $462 to $582 daily (bed rates) for pediatric acute care. California has no community-based skilled nursing facilities for pediatric patients.

*Cardiopulmonary Resuscitation Policies and Ethics*

In 1978 we noted great variations in the availability of resuscitation equipment, the training of personnel, and staff

attitudes toward cardiopulmonary resuscitation (CPR) for children with severe disabilities.[1] Today all personnel are trained in CPR, and all five centers have active "code blue" teams, often in association with local community fire-rescue departments, or paramedic units, or both. Advanced cardiorespiratory resuscitation and life support have also become automatic interventions for cardiorespiratory arrest.

In all California state developmental centers, CPR is routinely initiated when a cardiorespiratory arrest occurs, regardless of the client's medical diagnosis and prognosis, general state of health, and nature of disability, unless the client has a preexisting do-not-resuscitate (DNR) order. Of 865 children residing in five studied developmental centers, only 2 (both residing on the same unit) had DNR orders. One was an infant with major congenital anomalies, including holoprosencephaly. The second was an adolescent in a chronically vegetative state due to massive brain injuries received in a motor vehicle accident, whose ventilator support had been withdrawn by court order initiated by his parents in another hospital several months previously.

For a DNR order, the California DDS policy requires written concurrence of parents or close relative, guardian, or conservator; the physician in charge of the resident's care; a second staff physician; the medical director; and the executive director. The order must be written in the clinical record with documentation of the medical situation and a statement summarizing the outcome of consultations with the legal guardian, conservator, or family.[5] If parents or guardians request a DNR order that has not been recommended by this mechanism, they must be informed by the client's rights representative of their right to judicial recourse. Each center has a bioethics committee with membership appointed by the executive director, but the committee functions in an advisory capacity at the discretion of the medical director and is not routinely involved in every DNR review at each center.

Many concerns, including those of an ethical nature, were expressed regarding the residential care of children infected with the human immunodeficiency virus (HIV). Only one pediatric client (now deceased) in the five centers was diagnosed as having the acquired immunodeficiency syndrome (AIDS). It was noted that information regarding HIV status was available only to the medical director. The state DDS guidelines and program implementation for training employees in the care, treatment, and training of residents with an HIV-positive antibody status, HIV-related infections, and AIDS were developed after the conclusion of our site visits.

## Discussion

With the exception of the 11 children who were ventilator-dependent, we found the 441 technology-dependent children to be remarkably similar in their health care needs. Certainly the categories of technologic assistance and specific nursing care needs varied, as did individual diagnoses, medications, and program interventions. Of the 291 children with feeding gastrostomies, an estimated 60 resided in the developmental centers simply because the gastrostomy is a device for which the California licensing division requires 24-hour, in-home, skilled nursing care. Specialized foster home or family care home placement in the community is not available for most children with feeding gastrostomies. As physicians experienced in caring for children with various disabilities, we questioned the necessity for including persons with feeding gastrostomies (the device most commonly producing technology dependence) among those requiring the same level of nursing care as tracheostomy-dependent patients.

We recommended that the state DDS work with licensing authorities to alter nursing care requirements (such as those for gastrostomy care) and to develop new alternative care resources in the community for technology-dependent children. In the year since our report, state legislation was enacted permitting certain foster children with feeding gastrostomies to be cared for by adequately trained foster parents. We anticipate that this population will continue to expand as more children with AIDS suffer severe developmental disabilities due to central nervous system disease and as continuing technologic advances produce more survivors of a variety of insults that have left them neurodevelopmentally devastated.

We are impressed with the influence of ethical issues relating to the long-term care of this population of children with chronic disabilities, all of which are incurable but many of which are not imminently life-threatening. We recommended that the state DDS review its DNR policies and consider limitations on the routine administration of advanced CPR for select cases when requested by a child's program physician and family or guardian. In the year since our report, this has occurred.

Residential care facilities must scrupulously comply with legal and ethical mandates to provide care for their clients and to ensure that they are not discriminated against on the basis of their handicaps. Because the US Supreme Court in 1986 ruled against the "Baby Doe" regulations[6] under section 504 of the 1973 Rehabilitation Act, the regulations under the 1984 amendments to the Child Abuse Prevention and Treatment Act[7] remain in effect. Nonetheless, the Supreme Court stipulated that the Secretary of the US Health and Human Services could require state agencies to continue documenting their compliance with section 504,[8] suggesting that state hospitals and developmental centers may need to be more demanding than other hospitals in their accountability for DNR policies.[9] We are concerned that the denial of a consideration of DNR orders in certain cases (where there is a judicious medical indication and parental support of the decision), simply because a person resides in a state developmental center, might in itself be considered discriminatory.

More interaction with local medical communities was a consistent and convincing need. The medical staffs at developmental centers should have visible and active roles in medical education at various levels—that is, medical school, residency, and continuing medical education—so that pediatricians in local communities can benefit from the experience of physicians caring for these technology-dependent children who now reside in institutions but are becoming increasingly evident in community practice.

Finally, we asked whether the cost of residential care for these 441 technology-dependent children was actually a "bargain." As used in a discussion on individualized case management by the Task Force on Technology Dependent Children, "cost avoidance" described cost savings through the "effective and efficient organization and utilization of resources . . . and reducing potentially avoidable re-institutionalization."[10] For the technology-dependent children in our study, there is no care alternative other than an acute care hospital or intensive care unit. The developmental center

functions as an expensive alternative to an even more expensive hospital unit and, in this sense, is a bargain. Also, developmental center costs of care included an impressively comprehensive array of program components, such as basic facility or housing fees; 24-hour skilled nursing and physician services; laboratory, dental, x-ray, and other ancillary health care services; medical equipment; oxygen; special diet; clothing; special education programs; field trips; and even personal radios and cassette players for clients.

Costs of care and cost-avoidance issues are inherent in the establishment of new categories of community-based skilled nursing facilities designed to care for children who are technology dependent, profoundly mentally retarded, and who have complex medical and nursing needs that must be dealt with on an individualized basis.[11] Our concerns in this area are reflected in the ten-year experience of the Gothenburg, Sweden, study of care needs for 53 profoundly mentally retarded children with other complex health problems.[12] Despite the 1986 Swedish law making the care of mentally handicapped children in a hospital or institution unacceptable, 15% to 20% of Sweden's severely mentally retarded population need hospital-supported special care resources and 10% need some form of permanent care. The Swedish study calculated a need for about 10 to 12 beds per county (average population, 300,000) as the minimum to meet demands for permanent, respite, and other temporary residential care for these children with care needs and disabilities comparable with those of the 441 medically fragile, technology-dependent children residing in California developmental centers. Using the Swedish statistics to estimate beds needed, the number of such medically needy, severely mentally retarded children in California would range from 580 to 800—based on 58 counties and a state population of about 24 million—suggesting success with the ongoing efforts of developmental disabilities services in restricting state developmental center placement to those children who have severe and profound disabilities and for whom no alternative care resources exist.

## Summary

Our goal to find a trend toward a more severely involved, more medically needy pediatric population in the California state development centers was more than realized by finding 51% of the resident children and youth in acute and skilled nursing care programs (from birth to 22 years of age) to be technology dependent. This is a new resident population of children with severe developmental disabilities and complex health care needs. They survive because of technologic advances and excellent ongoing nursing and medical care and because of the societal developments and policy directives of the past decade that have made these resources available. The description of this population of children is a sobering reminder of the vast ethical and economic dilemmas confronting those in positions of setting policy for their care and of the ongoing challenges faced on a daily basis by those health care and other professionals who provide the total dependent care that they require. Each of these 441 technology-dependent children also compels us to address issues of prevention and of the personal tragedy and loss to families and society. They also emphasize the immediacy of the requirement for a better understanding of the finite limits of current health care resources and for the development of appropriate care alternatives.

Today, 10% of the nation's population resides in California, and we suspect that our findings reflect national trends toward an expanding population of technology-dependent, chronically disabled children living in hospitals, chronic care facilities, and in the community. In 1987, the Office of Technology Assessment predicted a 100% increase in "the next few years" in the number of technology-dependent children requiring ventilator assistance, parenteral nutrition or prolonged intravenous drug infusions, and other device-based respiratory or nutritional support.[4] In the year (as of May 1989) since these data were gathered, a waiting list of 20 children requiring ventilator assistance has begun for the dozen ventilator beds in California state developmental centers. We anticipate that these trends will continue and that, as our expanding medical technology makes it possible to resuscitate and maintain life for an increasing number of infants and children who would not have survived in the past decade, this population will grow. The implications of our findings for planning and program development in California are important and may be considered relevant to these issues from a national perspective.

### REFERENCES

1. Fremont AC, Wallace HM, Crain L, et al: Medical and health care in state residential institutions for children and youths. West J Med 1981; 134:80-86

2. Accreditation Manual for Hospitals, 1988. Chicago, Joint Commission on Accreditation of Hospitals, 1987

3. Residential Program Accreditation Manual. Boston, Accreditation Council on Services for People With Developmental Disabilities, 1987

4. Hospital vs Home Care—A Technical Memorandum, OTA-TM-H-38. Washington, DC, US Congress Office of Technology Assessment, Technology-Dependent Children, March 1987

5. Life Sustaining Procedures/Do Not Resuscitate Orders, Policy memorandum #121. Sacramento, California Department of Developmental Services, Developmental Centers Division, April 15, 1988

6. US Department of Health and Human Services: Nondiscrimination on the basis of handicap in relating to health care for handicapped infants. Federal Register 1984; 49:1622-1654

7. US Child Abuse Protection and Treatment Amendments of 1984, Pub L No. 98-457, Part B: Services and Treatment for Disabled Infants §§121 & 122 (Oct 9, 1984)

8. Otis Bowen v American Hospital Association, et al, 106 SCt 2101, No. 84-15-9 (Jun 9, 1986)

9. Kopelman LM, Irons TG, Kopelman AE: Neonatologists judge the 'Baby Doe' regulations. N Engl J Med 1988; 318:677-685

10. Report to Congress and the Secretary by the Task Force on Technology Dependent Children, HCFA publication No. 88-02171. US Department of Health and Human Services, Health Care Financing Administration 1988; 2:35

11. Cohen HJ, Biehl R, Crain LS, et al, Committee on Children with Disabilities: Transition of severely disabled children from hospital or chronic care facilities to the community. Pediatrics 1986; 78:531-534

12. Hagberg B, Edebol-Tysk K, Edström B: The basic care needs of profoundly mentally retarded children with multiple handicaps. Dev Med Child Neurol 1988; 30:287-293

# Radiologic Case

## A 36-Year-Old Woman With a Pulsatile Mass of the Left Tympanic Membrane

JODY REISER, *Tucson;* KELVIN S. DANIELSON, MD; JONATHAN M. LEVY, MD; RICHARD D. ZONIS, MD; *and* FRED K. CHRISTENSEN, MD, *Scottsdale, Arizona*

*A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.*

JONATHAN M. LEVY, MD
Series' Editor

*A 36-year-old woman complained of a "humming sound" in the left ear for ten weeks. On otoscopic examination, a red, pulsatile mass was seen extending from the left tympanic membrane into the external auditory canal. A cranial nerve examination elicited no abnormalities. On audiologic examination there was a mild conductive hearing loss on the left. Axial and coronal computed tomographic (CT) scans of the head were done (Figure 1).*

What is the diagnosis?

What is the prognosis?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

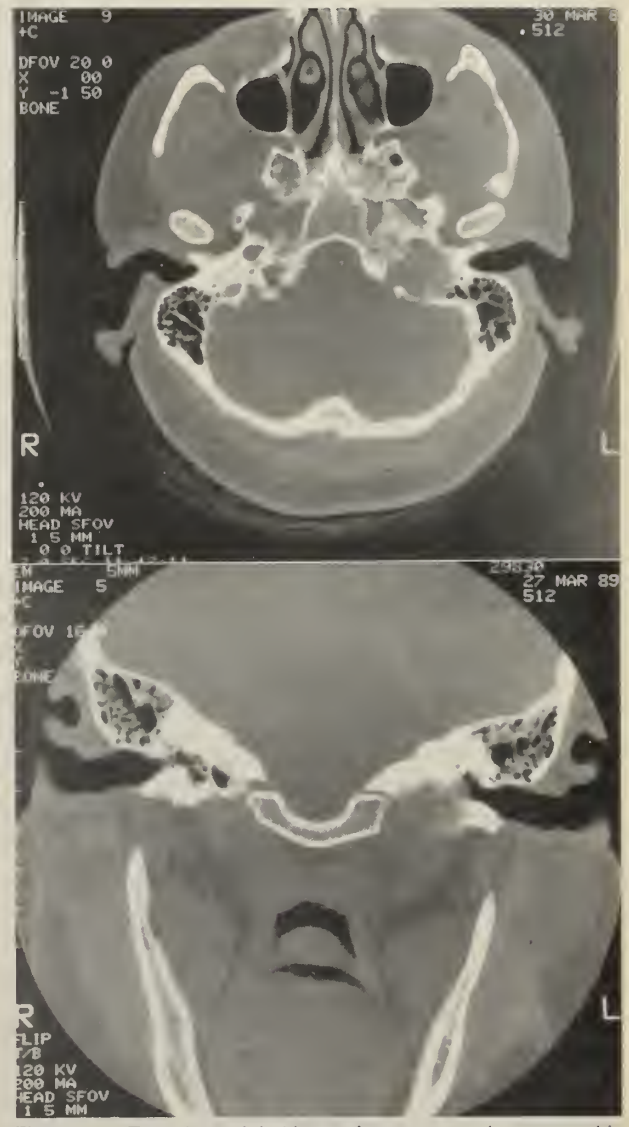



**Figure 1.—Top,** An axial thin-section computed tomographic scan shows the base of the brain. Compare the bony structures medial to the external auditory canals. **Bottom,** A coronal scan is taken at the same level.

(Reiser J, Danielson KS, Levy JM, et al: A 36-year-old woman with a pulsatile mass of the left tympanic membrane. West J Med 1990 Apr; 152:439-440)

Ms Reiser is a fourth-year medical student at the University of Arizona Health Sciences Center, Tucson. From the Departments of Diagnostic Radiology (Drs Danielson and Levy), Otolaryngology (Dr Zonis), and Neurosurgery (Dr Christensen), Scottsdale Memorial Hospital, Scottsdale, Arizona.

Reprint requests to Jonathan M. Levy, MD, Department of Diagnostic Radiology, Scottsdale Memorial Hospital, 7400 E Osborn Rd, Scottsdale, AZ 85251.

# DIAGNOSIS: Glomus jugulare tumor

THE AXIAL CT SCAN (Figure 1, top) shows a mass that arises from the left jugular foramen, extending into and destroying a portion of the petrous bone. On the coronal scan (Figure 1, bottom), the mass can be seen bulging into the external auditory canal. The structures of the middle ear are spared. A carotid angiogram (Figure 2) shows a 3- by 5-cm hypervascular mass that was fed by occipital and deep facial branches of the external carotid artery. The mass extends into the infratemporal fossa. A pulsatile mass in this anatomic area is most likely a glomus jugulare tumor. Other possibilities, excluded by the combination of CT and arteriography, include glomus tympanicum tumor, dehiscent jugular bulb, and aberrant internal carotid artery.

Glomus jugulare tumors arise from the glomus cells in the adventitia of the jugular bulb. They are benign, slow-growing vascular lesions that are locally invasive. They occur predominantly in middle age and are more common in women. Patients complain of buzzing or ringing in the ears (tinnitus), often pulsatile in nature. Hearing loss is a frequent finding. More than one cranial nerve may be involved if the tumor is large. Endocrine activity mimicking pheochromocytoma or the carcinoid syndrome has been reported.

The diagnostic evaluation of a patient with a glomus tumor typically begins with an otologic examination. The tumor can often be seen pulsating behind the tympanic membrane, as in our patient. High-resolution, contrast-enhanced CT scans are highly sensitive for showing the osseous changes of the skull base produced by tumor erosion. Magnetic resonance imaging is superior to CT in demonstrating the vascularity and three-dimensional relationships of the tumor. Computed tomography, however, remains the study of choice for showing the pathognomonic osseous changes. Angiography best depicts the vascular character of the tumor and is important preoperatively for evaluating jugular vein patency and carotid artery involvement.

The prognosis of patients with glomus jugulare tumor is generally good. The first line of treatment is surgical, with total resection if the tumor is small and staged removal if there is extension into the posterior fossa. Postauricular, transmastoid, and infralabyrinthine approaches are used, depending on the exact position and size of the mass. Preoperative embolization has been used to devascularize the tumor and aid in hemostasis. Older patients, those with contraindications to a surgical procedure, and patients previously treated surgically who have recurrence benefit from radiation therapy. Irradiation induces a vasculitis, which halts tumor progression. Recurrence rates following radiation treatment are approximately 15% at five years. Our patient has recently had her operation and is recovering.

**Figure 2.**—A left carotid arteriogram shows a densely vascular mass **(arrows)** in the left petrous bone with a typical appearance of a glomus jugulare tumor.

### GENERAL REFERENCES


Brackman D, Kinney S, Fu K: Glomus tumor: Diagnosis and management. Head Neck Surg 1987; 9:306-311

Larson TC, Reese DF, Baker HI Jr, et al: Glomus tympanicum chemodectomas: Radiographic and clinical characteristics. Radiology 1987; 163:801-806

Phelps PD, Lloyd GA: Vascular masses in the middle ear. Clin Radiol 1986; 37:359-364

Swenson MR, Sibley W: Glomus jugulare tumor. Postgrad Med 1982; 72:213-214

# In the Forefront

# Developing Principles for Prudent Health Care Allocation

## The Continuing Oregon Experiment

RALPH CRAWSHAW, MD, *and* MICHAEL GARLAND, DScRel, *Portland;* BRIAN HINES, MSW, *Salem, Oregon; and* BARRY ANDERSON, PhD, *Portland*

*I have come across several types of associations in America of which, I confess, I had not previously the slightest conception, and I have often admired the extreme skill they show in proposing a common object for the exertions of very many and in inducing them voluntarily to pursue it.*

ALEXIS DE TOCQUEVILLE
*Democracy in America*, 1840

Allocating scarce health care resources imposes elemental choices on a democracy. Who makes the immediate choices—patient, clinician, administrator, or politician—varies with circumstances, but in a representative democracy the ultimate choices devolve on the citizens. Directly or indirectly, citizens supply both the funding and the moral base for the delivery of health care. The question of how citizens make, or should make, the judgments required for the prudent allocation of health care resources merits careful consideration by all.[1] These problems have been faced by the people of Oregon, and we describe the community dialogue process used to uncover public policy principles for setting health care priorities.

### Process for Consensus Building

"Oregon Health Priorities for the 1990s" was a project of Oregon Health Decisions (OHD),[2] supported by a grant from the Robert Wood Johnson Foundation, to determine which health services citizens considered the most important and therefore of the highest priority for government funding.[3,4] Oregon Health Decisions is a citizen network dedicated to raising public awareness of bioethical problems. To bring the issues of allocating health care resources to citizens, in 1987 OHD used the following steps:

A steering committee, chaired by the president of the state senate, John Kitzhaber, MD, established a specific methodology and agenda of allocation issues to be discussed at local forums. Community meetings were organized throughout the state to stimulate citizens' awareness of these issues and a search for consensus. The consensus from the different community meetings was refined and collated by OHD staff into resolutions focusing on public policy congruent with expressed citizen values. These resolutions were presented to a Citizens' Health Care Parliament where they were received and amended by representatives of the community meetings, of government, and of private organizations. The parliament's resolutions were then published by OHD and circulated among public and private policy makers. The civic and humanitarian impact of the project is monitored by an implementation committee that provides testimony to the state legislature. Finally, OHD staff identifies related future projects.

#### *Community Meetings*

During the course of the project, 19 meetings were held across the state of Oregon. They were usually convened in the evening, lasted two hours, and were aimed at the general public (although several of the meetings were presentations to special groups). Settings included a community college, restaurant meeting rooms, hospitals, churches, and a synagogue. Notices of the open community meetings were broadcast through such means as direct mailings, radio spots, newspaper articles, civic organizations, and word of mouth.

A total of 560 people completed a survey developed by the staff that was the centerpiece of the "Oregon Health Priorities for the 1990s" meetings. Table 1 shows some of the demographic characteristics of the respondents.

With few exceptions, the meetings followed a standard format. The attendees were seated in small groups to facilitate essential dialogue. A locally trained facilitator was assigned to each group to focus discussion and ensure that the group's major concerns would be reported to the meeting as a whole. A local medical or political leader gave a welcoming introduction, then turned the meeting over to a project staff member. The problem of health care resource allocation was presented to the attendees as a kind of Chinese box problem: open up one box, and you find another; study one level of the allocation problem, and you are led to another level.

The outermost level concerns the priority that health care should receive in comparison to other social needs. Given its emphasis on public policy, the Oregon Health Priorities for the 1990s project survey framed this question in terms of the share of the state government budget allocated to health services. Meeting participants were shown how the budget dollar currently is split among seven areas—economic development, education, health services, non-health human resources programs, natural resources, transportation, and all others—and then asked to indicate whether they wanted to have more money, the same amount of money, or less money spent in each area. They were also asked whether they

(Crawshaw R, Garland M, Hines B, et al: Developing principles for prudent health care allocation—The continuing Oregon experiment. West J Med 1990 Apr; 152:441-446)

From the Departments of Psychiatry (Dr Crawshaw) and Public Health and Preventive Medicine (Dr Garland), Oregon Health Sciences University School of Medicine, and the Department of Psychology, Portland State University (Dr Anderson), Portland. Mr Hines is a health policy consultant in Salem, Oregon.

Reprint requests to Ralph Crawshaw, MD, 2525 NW Lovejoy, Portland, OR 97210.

wanted more taxes, the same taxes, or less taxes levied to pay for any or all of these state government programs. This provided them the option of changing the way the state budget "pie" was sliced, changing the size of the entire pie, or both.

It turned out that 69% of the meeting participants favored more money going to health services, with 24% favoring the same, and 3% less. It is recognized that more than half of the attendees worked in health care, and most of the others had some special interest in this area by virtue of their attendance. Education was the only other area in which a majority (51%) wanted more money spent. The only area where most (51%) wished less spent was the "all other" category: administrative, legislative, and judicial branches.

Health services and education account for 42 cents of every dollar spent by Oregon state government, while "all other" accounts for 16 cents. It is apparent that savings in the last category would not go far toward increasing the allocation to the first two. Furthermore, only 33% of the survey respondents favored increasing taxes to permit more money to be spent on the programs they felt most important, without cutting others. Thus, people generally wanted more money to be spent on health services, yet did not identify where these funds should come from—a familiar scenario for legislators. A central goal of the meeting process was to help community participants move beyond "magical" thinking that expects resources to be available without difficult tradeoffs.

The next level of the health care allocation question concerns what general priorities should be assigned within the health sector. Citizens' values in this area were determined by a matrix of 16 "health care building blocks" (Figure 1). In this matrix the human life cycle (infants, children, adults, and the elderly) is one axis, and the type of health service (critical, short-term, long-term, preventive) is the other. After being given definitions of the building blocks, meeting participants were asked to assign a priority to each block: five "highs," six "mediums," and five "lows."

Interestingly, even this hypothetical paper-and-pen exercise in allocating health care resources met with considerable resistance from some participants. A few even refused to complete this portion of the survey, arguing they wanted to give all the blocks high priority. Most people, however, were willing to complete the exercise despite the discomfort, which appeared to be an accurate reflection of an overall social attitude in this area: while there is an intellectual recognition of the need to set health care priorities, when the reality sets in that life-and-death decisions are being made, some degree of misgiving frequently becomes evident. Experiencing this uneasiness proved essential to the process as it became a major stimulus for group discussion that followed the priority-setting exercises.

Figure 2 shows the priorities that resulted by averaging the 560 individual surveys. Preventive care for infants, children, and adults received three of the five "high" priorities, with critical care for children and long-term care for the elderly receiving the others. Those who hope to avoid intergenerational conflict in health care allocation will be heartened to know that, on average, those younger than and those older than 65 assigned different priorities to only 4 of the 16 blocks. Interestingly, even the elderly consider critical care for their own age group to be a low priority (15th out of 16). Those older than 65 also consider preventive care for infants and children and critical care for children to be of higher priority than long-term care for the elderly (which rated 4th of 16).

Somewhat greater differences were evident between those participants who worked in health care and those who did not. Critical care tended to be given a somewhat higher priority by non-health care professionals and preventive care a higher priority by those working in the health field. This was reflected in the final question asked of the meeting participants: "Looking specifically at one of the types of 'critical care,' should Oregon state government pay for heart, liver,

TABLE 1.—*Characteristics of Survey Respondents, N=560*

| *Characteristic* | *Respondents, Number* | *Percent* |
|---|---|---|
| Age, years | | |
| Under 25 | 28 | 5 |
| 25-44 | 269 | 48 |
| 45-64 | 174 | 31 |
| 65 and over | 73 | 13 |
| No response | 16 | 3 |
| Sex | | |
| Male | 196 | 35 |
| Female | 358 | 64 |
| No response | 6 | 1 |
| Work in health care | | |
| Yes | 314 | 56 |
| No | 230 | 41 |
| No response | 16 | 3 |
| Political leaning | | |
| Conservative | 112 | 20 |
| Middle of the road | 263 | 47 |
| Liberal | 163 | 29 |
| No response | 22 | 4 |

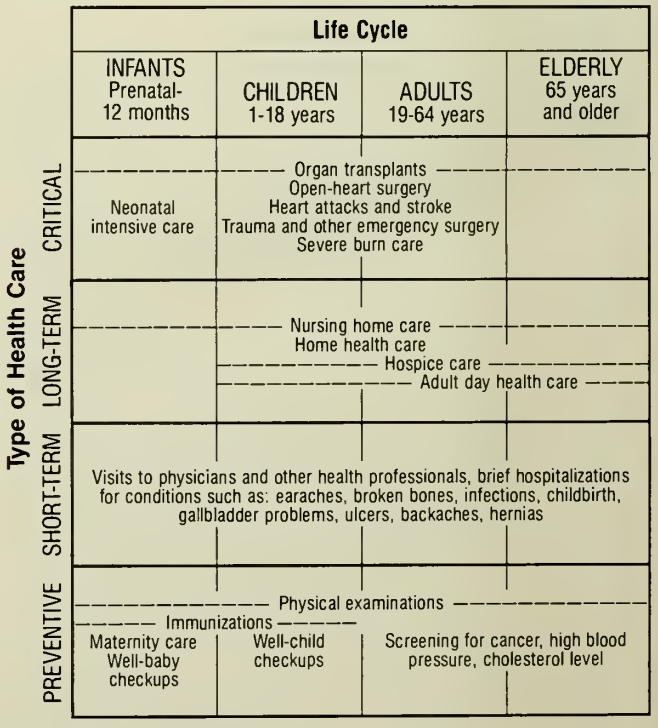



**Figure 1.**—The 16 squares show the types of health care services required at the various stages of the life cycle: critical = care for acute life-threatening conditions; long-term = care for chronic or disabling conditions; short-term = care for acute, not life-threatening conditions; and preventive = prevention or early detection of ill health.

| Health Care | Life Cycle | | | |
|---|---|---|---|---|
| | INFANTS | CHILDREN | ADULTS | ELDERLY |
| CRITICAL | **Medium** | **High** | **Medium** | Low |
| LONG-TERM | Low | Low | **Medium** | **High** |
| SHORT-TERM | **Medium** | **Medium** | **Medium** | Low |
| PREVENTIVE | **High** | **High** | **High** | Low |

**Figure 2.**—The results of a survey are given in which the types of health care shown in Figure 1 were assigned ratings of high, medium, or low priority.

and bone marrow transplants for Medicaid clients?" Here Oregon Health Priorities for the 1990s touched a nerve sensitized to resource allocation issues by the public concern for Coby Howard whose mother was denied Medicaid funding for a bone marrow transplant, namely the discrete services that should and should not be made part of an adequate benefit package.

Overall, 20% favored state payment for organ transplants, 41% were opposed, and a large percentage—39%—were unsure or did not respond to the question. Of the health care workers, however, 51% opposed such funding compared with only 36% of the non-health care workers. We cannot say whether this is due to a fundamental difference between health professionals and the general public in how critical care or "welfare medicine" is viewed or to discrepancies in factual information held by the two groups.

The political inclinations of respondents influenced the level of priority health care in the state budget. Of self-described conservatives, 58% wanted more dollars for health care, as opposed to 70% of "middle-of-the-road" people and 82% of liberals. A similar trend was evident in the question of whether total state government spending should be increased through higher taxes: 16% of conservatives said yes, as opposed to 40% of middle-of-the-roaders and 72% of the liberals.

At each meeting, following the completion of the individual survey, facilitators tabulated the responses of the six to eight people seated in each small group. Colored stickers were used to graphically indicate a group's high, medium, and low priorities on the building block portion of the survey. A 30-minute discussion period ensued during which the facilitator probed for the reasoning behind individual value judgments, trying to bring about agreement through consensus before voting on the group's final priorities.

Each group then reported their conclusions to the entire meeting. Colored markers were placed on a large magnetic board to graphically indicate the extent of agreement among the small groups. After the program closed with a general discussion of the findings, project staff collected the individual surveys and notes summarizing the small group discussions that had been recorded by the facilitators. Qualitative and quantitative analyses of this information were carried out to uncover the values that underlay the survey responses, a necessary precursor to the development of general policy recommendations by a Citizens' Health Care Parliament.

Participants in the local meetings were asked to set health care priorities without much guidance as to *how* to do so. Each person was free to apply his or her own values and common sense to the task at hand. Yet, even when breakdowns of the survey responses are made for age, sex, political leanings, and whether one works in health care, the extent of agreement on at least the 16 building block priorities was surprising. Apparently most participants were basing their priorities on a relatively similar set of moral principles, even though these principles were largely unspoken and possibly unrecognized at a conscious level. It is one thing to say *what* we prefer, and another to be able to say *why*. Some examples show how the project staff threaded their way through the "whats" in search of the "whys."

*What:* The area of preventive health care received three of the five "high" priorities. So it appears that, in general, prevention is the most highly valued type of health service. *Why:* Based on written and verbal comments made by the meeting participants, a key reason given was that prevention leads to health benefits being achieved at the lowest cost (compared with treating problems after they occur). Thus the greater efficiency, or benefits received per dollar spent, the greater the value of the health service.

*What:* Notwithstanding the preceding observation, preventive care for the elderly was given a "low" priority—as were short-term and critical care for the elderly. *Why:* Based again on comments, the primary reason for this appears to be that younger people have more years of remaining life to gain or lose as a result of getting, or not getting, effective, short-term, and critical services. Thus, the greater the number of years added to life, the greater the value of the health service.

*What:* Long-term care for the elderly, however, was given a "high" priority. *Why:* Meeting participants seemed to believe that good long-term care can produce a marked increase in the quality of life for the elderly (along with some effect on the length of life). Quality of life was viewed, in part, as the degree to which a person is able to live as independently as possible. Thus, the greater the increase a health service makes in the quality of life, the greater the value of that service.

### *Citizens' Health Care Parliament*

In September 1988, a total of 50 delegates (24 selected from participants in the community meetings, 15 appointed by county commissioners, and 11 representatives from various civic organizations—a firefighter, a homemaker, a retired lawyer, a county commissioner, a nurse, an insurance salesperson, and others in diverse occupations) assembled in Portland, Oregon. They were supplied with the findings from the community meetings and a set of proposed principles that the staff had distilled as the underlying values used by community meeting participants in assigning their priorities.

The parliament, in session for a day and a half, began with a half day of small-group interaction during which the delegates explored their concept of "quality of life" in personal terms. This exercise proved important, as quality-of-life considerations often are dismissed as too subjective to be useful in public considerations. The discussion was also crucial for building a sense of community among delegates because it helped them share deeply held beliefs. The small groups concluded this portion of the parliament by examining the staff's proposed resolutions, considering how they were derived as well as clarifying and editing them in preparation for the next day's parliamentary debate.

The parliamentary meeting lasted eight hours. Each principle was introduced as an individual resolution followed by open debate according to *Robert's Rules of Order.* After the

members were satisfied that all sides of the issue had been explored, they voted on that resolution and then passed to the next, through all 15 resolutions.

The parliament delegates repeatedly sought to balance the benefits resulting from extended quantity of life against those that accompany improved quality of life. The proposed principles reflect the ongoing need for both of these closely intertwined potential benefits to be kept in mind by anyone assessing the value of health services.

*Resolutions*

Through its stated resolutions or principles, which were hammered out in open debate by the 50 delegates, the parliament addressed how society and government in particular should go about determining both the relative value of health services compared with other social needs and priorities within the health care arena. Four general areas emerged:

- The role of government in health care is to maintain and improve the overall quality of life. Public decision makers should keep in mind the balance between length of life and quality of life when addressing the multidimensional nature of health care services.
- The need for priorities exists so long as the public's demand for health services exceeds its capacity, or willingness, to fund through third-party financing. Consequently, community consensus is necessary in deciding which services will be funded.
- The process of the equitable determination of health care priorities demands broad participation by providing open, public forums that focus on maximizing the effective use of limited funds.
- While clinical judgments remain in the domain of experts, value judgments of the general public must be inte-

## Principles for Health Care Resource Allocation

### Purposes of Health Services

1. The responsibility of government in providing health care resources is to improve the overall quality of life of people by acting within the limits of available financial and other resources.
2. Overall quality of life is a result of many factors, health being only one of these. Others include economic, political, cultural, environmental, aesthetic, and spiritual aspects of a person's existence.
3. Health-related quality of life includes physical, mental, social, cognitive, and self-care functions, as well as a perception of pain and sense of well-being.
4. Allocations for health care have a claim on government resources only to the extent that no alternative use of these resources would produce a greater increase in the overall quality of life of people.
5. Health care activities should be undertaken to increase the length of life, the health-related quality of life, or both, during a life span.
6. Quality of life should be one of the ethical standards when allocating health care resources involving insurance or government funds.

### Why Priorities Need to be Set

7. Every person is entitled to receive adequate health care.
8. It is necessary to set priorities in health care, so long as health care demands and needs exceed society's capacity, or willingness, to pay for them. Thus, an "adequate" level of care may be something less than "optimal" care.

### How to Set Health Priorities

9. Setting priorities and allocating resources in health care should be done explicitly and openly, taking careful account of the values of a broad spectrum of the Oregon populace. Value judgments should be obtained in such a way that the needs and concerns of minority populations are not undervalued.
10. Both efficiency and equity should be considered in allocating health care resources. Efficiency means that the greatest amount of appropriate and effective health benefits for the greatest amount of persons are provided with a given amount of money. Equity means that all persons have an equal opportunity to receive available health services.
11. Allocation of health resources should be based, in part, on a scale of public attitudes that quantifies the tradeoff between length of life and quality of life.
12. In general, a high priority for health care activity is one where the personal and social health benefits:costs ratio is high.
13. The values of the general public should guide planning decisions that affect the allocation of health care resources. As a rule, choices among available alternative treatments should be made by the patient, in consultation with health care providers.
14. Planning or policy decisions in health care should rest on value judgments made by the general public and those who represent the public and on factual judgments made by appropriate experts.
15. Private decision makers, including third-party payers and health care providers, have a responsibility to oversee the allocation of health care resources to assure their use is consistent with the values of the general public.

**Figure 3.**—These principles were adopted by the Citizens' Health Care Parliament, September 23 to 24, 1988, Portland, Oregon.

grated with expert technical judgments to produce practical, prudent, and fair health policy. Decision makers in the private sector should seek to allocate resources in a manner consistent with community values (see Figure 3).

The community health decisions process revealed that the balance between quality-of-life and quantity-of-life valuations is central to the way in which citizens assess health care priorities. This balance is made explicit in Resolution 11: "Allocation of health resources should be based, in part, on a scale of public attitudes that quantifies the trade-off between length of life and quality of life." This dynamic process does not abrogate the role of the physician-patient relationship in deciding allocations, for Resolution 13 states in part, "As a rule, choices among available alternative treatments should be made by the patient, in consultation with health care providers," and Resolution 14 goes on, "Policy decisions in health care should rest on value judgments made by the general public and those representing the public, and on factual judgments made by appropriate experts."

*Influence on Public Policy*

The full set of principles was published and sent to all state legislators, producing an active interface between Oregon Health Decisions and the Oregon legislature. Following the parliament and before the meeting of the 1989 legislative session, Senate President Kitzhaber secured a grant from the Fred Meyer Charitable Trust to test one approach for setting health care priorities. Panels of health care providers were asked to prioritize services using the same life-cycle conceptual approach developed by the Oregon Health Priorities for the 1990s project. Many of the principles established by the Health Care Parliament are reflected in two bills. By creating a Health Services Commission requiring decisions on setting priorities for health care resources through the community meeting process for determining values, Senate Bills 27 and 935 outline a general mechanism for setting health care priorities in Oregon. Senate Bill 27 incorporates the health decisions process, stating, "In conjunction with the Joint Legislative Committee on Health Care, the Commission shall actively solicit public involvement by a community meeting process for consensus on the values to be used to guide health allocation decisions."

The second bill, Senate Bill 935, is intended to fill the gap in funding for the uninsured working poor who cannot afford adequate health insurance and yet are not covered by any form of government-mandated health insurance. This bill offers tax credits to small businesses with 24 or fewer employees to purchase health coverage for their employees from the state-operated Insurance Pool Governing Board at a benefit level comparable to that determined through Senate Bill 27 for Medicaid recipients. The bill mandates that by 1994 all employers must offer this coverage. Senate Bill 935 will result in insurance being available for approximately 100,000 to 120,000 working people who would otherwise have no health care coverage. Under these new laws, the Health Services Commission will be responsible for evaluating the cost-effectiveness of all Medicaid services through relevant information from experts while reaching out to citizens' health care values through community meetings.

## Discussion

The commonplace complaints that the public is unrealistic in its expectations for health care services, that the tax base for funding care to the poor is inadequate, that the cost and complexity of medical technology grow exponentially, and that government leaders avoid addressing resource allocation issues frequently end with a lament that national, state, and local health policy is adrift. Simultaneously, as evidence grows that without the benefit of moral values, economic necessity forces health care allocation decisions affecting the poor, the citizenry becomes uneasy. The uneasiness grows as citizens seek a response from a system apparently devoid of reasonable direction, control, and leadership. Finally, when faced with the arcane language of health care experts and mind-boggling costs of medical technology, citizens' concerns fester into outspoken frustration. Patently, the nation resists accepting the invisible forces of the marketplace as the ultimate judge of who shall and shall not have health care services.

In part, the citizens' default in judging the allocation of health care resources can be traced to the failure of the federal government's health planning effort. In 1974, federal legislation in the form of Public Law 93-641, the National Health Planning and Resources Development Act, was enacted to empower the public, designated as "consumers," to curb a cost-*in*effective health care system. The general public was expected to constrain an overbuilt hospital system through federally mandated health planning agencies. These organizations were operated at three levels, with "subarea councils" at the county level answering to regional "health systems agencies" that in turn reported to a statewide Health Coordinating Council. Each of the 50 states developed a plenitude of health planning organizations intended to cap the uncontrolled capital outlay for hospitals and medical technology through informed citizen input. A decade later, the federal government quietly abandoned the program.

A reason for the failure of the federal effort locally was the absence of functional community forums in which citizens could hammer out practical health values. Though the health systems agencies meetings permitted the discussion of access and health status issues, their tightly prescribed agenda for reducing hospital costs failed to integrate essential public concerns for personal autonomy and justice in allocating resources. Neither the structure of the federal planning effort, nor the content, was open to public negotiation. With the moral concerns and values of the public omitted, health planning was never accepted as essential by the local communities. Devoid of genuine democratic input, the federal program proved doomed from its inception. In Oregon, citizens set out to salvage as much as possible from the collapsed federal program through Oregon Health Decisions, seeking a way that would include human as well as economic values.

History teaches that for our nation to effectively and morally allocate scarce health care resources that determine life and death, certain criteria must be met. First, there must be a publicly agreed-on need for the allocation. Understandably, society attempts to avoid making such choices by either denying the need or relegating the choices to the "invisible hand" of the marketplace. To deal effectively with the inescapable emotions and their consequent paralyzing of political will, consensus is indispensable. Second, the rules must be open and apply to all. Morally and politically, a democracy cannot long tolerate legislation that explicitly permits the rich to live at the expense of the poor. Third, actual life-and-death choices must be made as close to the local level as possible. In health care, this means as close to the

bedside, the patient, as possible. Because circumstances vary from region to region of our nation, the public resists regulations that attempt to direct uniformly and administer impartially specific cases from afar. Fourth, decisions must be open and appealable—self-evident in a democracy.

For the citizens of our nation to face openly a critical problem such as allocating scarce health care resources, the issue must meet the criteria for functional and moral acceptance by the public. To accomplish this, the public must be fully informed of the situation by our leaders and relevant experts in a language that is not only understandable but suitable for the public discourse. Only with a functional language and a meaningful forum can citizens explore the full moral consequences of allocation issues. Consequently, a search for consensus on health care priorities calls for citizen education and discussion of the full extent and meaning of the government allocation of health care resources.

## Conclusions

The project, Oregon Health Priorities for the 1990s, found that there is a surprisingly high degree of consensus among the involved citizenry regarding the principles by which the relative importance of general types of health services might be identified and, consequently, where cuts and enhancements in health services might be made. Through open community meetings, the inherent prejudices that come with fixed turf or allegiance to political parties were subordinated to an ongoing, self-adjusting source of community values that enjoys a broad commonality. A continuing process of valuing occurs that constructively contributes to anticipated changes in the health delivery system while sustaining the basic dynamic of judging between length-of-life and quality-of-life issues. Only direct citizen involvement can be expected to yield the necessary broad consensus.

### REFERENCES

1. Jennings B: A grassroots movement in bioethics. Hastings Cent Rep 1988 Jun/Jul; 18(Suppl):1-16

2. Crawshaw R, Garland M, Lobitz C, et al: Oregon Health Decisions—An experiment in community consent. JAMA 1985; 254:3213-3216

3. Crawshaw R: Organ transplants—A search for health policy at the state level. West J Med 1989; 150:361-363

4. Crawshaw R: 'Society Must Decide'—Oregon Health Decisions: Biovaluation beyond bioethics. West J Med 1986; 144:246-248

# Medical Ethics

## A Policy Concerning the Therapeutic Use of Human Fetal Tissue in Transplantation

ROBERT M. NELSON, MD, *San Francisco*

The transplantation of human fetal tissue into patients suffering from chronic and incurable diseases such as Parkinson's disease and diabetes mellitus appears to be a promising therapy worthy of further basic and clinical research.[1-4] Nevertheless, in May of 1988, Robert E. Windom, MD, Assistant Secretary for Health, US Department of Health and Human Services, imposed a moratorium on federally funded research concerning therapeutic transplantation using human fetal tissue obtained from induced abortions.[5] An outside advisory committee was created to examine the ethical and legal implications of transplantation research on human fetal tissue and of the therapeutic use of tissue from aborted fetuses.[6] Their report, issued in December of 1988, supported the use of human fetal tissue in transplantation; however, the ban on the federal funding of research using fetal tissue obtained from induced abortions has not been lifted and continues to disrupt clinical research.[7] Although a number of organizations have come out in support of the therapeutic use of human fetal tissue,[8,9] antiabortion activists continue to oppose the research. A clear division of the question concerning the appropriate use of human fetal tissue from the issue of abortion is necessary if research into the therapeutic use of human fetal tissue is to proceed.

A practical separation of induced abortion and the subsequent use of human fetal tissue, for the purposes of public policy, can be achieved. In this article I argue for a policy concerning the therapeutic use of human fetal tissue that would allow for the use of fetal tissue from induced abortions, provided that

- The commercial use or sale of the tissue is prohibited;
- Designation of the tissue recipient is forbidden;
- There is a clear separation of abortion counseling and management from the harvesting of fetal tissue; and
- Informed consent for the use of the fetal tissue is obtained.

The most controversial aspect of the proposed policy is the use of tissue from induced abortions, for otherwise it resembles aspects of our current ethical and legal understanding of cadaveric organ transplantation. The proposed policy does not require the endorsement of the "pro-life" position concerning the status of the fetus as person or the "pro-choice" reduction of the fetus to simply a part of a woman's body. The main argument is that once aborted, the fetal tissue can be used provided certain procedures are rigidly observed. The overall goal of the policy is to minimize and isolate the effects of the use of human fetal tissue from the incidence and performance of abortions.

The current restriction on the use of fetal tissue obtained from induced as opposed to spontaneous abortions suggests that the pivotal issue is not the use of fetal tissue per se, but the use of fetal tissue from induced abortions. Permitting the use of human fetal tissue from induced abortions is not only the most controversial aspect of the proposed policy, it is also the most central, for it eliminates fetal tissue as a scarce resource. By doing so, the inevitable temptation to use abortion as a means of obtaining scarce fetal tissue would be removed. Supply would exceed demand, thus reducing the economic incentives that contribute to the possibility and attractiveness of commercial exploitation. In addition, the fetal tissue from spontaneous abortions may be inappropriate for transplantation into a human subject.[6] Thus, it may be both ethically and medically unwise to restrict the therapeutic use of human fetal tissue to spontaneous as opposed to induced abortions.[6,8]

The ban on the commercial use or sale of human fetal tissue seeks to eliminate the opportunity for the commercial exploitation of pregnant women by third parties seeking to harvest fetal tissue, protect from product liability by viewing the transfer of fetal tissue as a service, and prevent the reduction of a fetus's status to that of a mere body part to be sold at a pregnant woman's discretion. A ban on the sale of fetal tissue is consistent with current policy that generally prohibits the sale of solid organs.[10] Although the legal and ethical justification for such a ban may be controversial, forbidding the sale of fetal tissue per se is consistent with a reluctance to base a woman's decisions concerning the fetus on a presumed property right.[11] Guidelines would need to be established governing the necessary financial aspects of the transfer of fetal tissue, such as appropriate fees for isolating, processing, storing, and then implanting the fetal tissue. The primary goal in banning the commercial use or sale of human fetal tissue, however, is to eliminate any role financial gain might play in potentially increasing the incidence of abortions.

Prohibiting the designation of the tissue recipient is aimed at preventing abortion from being used as a means for fetal tissue harvest by eliminating as a reason for the abortion the desire to donate tissue to a specified person. The personal benefit that may be realized by a woman in giving a gift of

(Nelson RM: A policy concerning the therapeutic use of human fetal tissue in transplantation. West J Med 1990 Apr; 152:447-448)

From the Division of Pediatric Critical Care, Department of Pediatrics, and the Program in Medical Ethics, University of California, San Francisco, School of Medicine.

Supported in part by a National Research Service Award in Bioethics from the National Center for Nursing Research, National Institutes of Health.

Reprint requests to Robert M. Nelson, MD, Division of Pediatric Critical Care, M-646, University of California, San Francisco, CA 94143-0106.

fetal tissue to a loved one is overshadowed by the fact that an abortion is the necessary means by which the gift is given.[12,13] Simply put, the fetus is not hers to give. Recognizing the fact that not all gifts are given freely, to prohibit the designation of the fetal tissue recipient would also eliminate the possibility of a woman being coerced by friends or family into becoming pregnant or undergoing an abortion (or both) as a means of providing fetal tissue.

There needs to be a clear separation of abortion counseling from any consent for the therapeutic use of fetal tissue. The ethical concern about a possible conflict of interest has led to the clear legal separation of the declaration of brain death from the procurement of organs for transplantation. In a similar fashion, the decision for an abortion, both on the part of a pregnant woman and her physician, needs to be kept separate from the desire for and the procurement of fetal tissue for donation. Though a woman may receive consolation from the belief that some good came from an otherwise painful and tragic situation, this consolation should not constitute a sufficient reason for seeking an abortion. In addition, all possible conflicts of interest on the part of the physician need to be eliminated, including issues of publication, research support, or patient referrals.[6] The management of the pregnancy, the decision to undergo an abortion for whatever reason, and the timing of the abortion should be independent of any discussion of the subsequent use of the fetal tissue. In particular, any modification of abortion technique in favor of procuring suitable fetal tissue at an increased risk to the pregnant woman should be excluded. Properly constructed, such a policy would not encourage women to seek abortions, or physicians to perform abortions, in order to donate or procure fetal tissue.

Finally, the policy would require informed consent in the disposition of fetal remains, whether for experimental or therapeutic purposes. Not only does this recognize the right of a woman to exercise control over her own reproductive process but also serves to elevate the status of the fetus above that of a mere pathologic specimen. The standard consent form for an abortion could include a section on the disposition of fetal remains, offering a choice between the immediate disposal or the use of the tissue for either experimental or therapeutic purposes.

In support of the therapeutic use of human fetal tissue, Jonsen has argued that abortion ought to be a secondary issue because salvaging tissue from a dead fetus is ethically similar to cadaveric organ harvest, for which consent may not be morally required.[14] (Note that current policy in the United States requires proxy consent for cadaveric organ harvest.) Opponents of abortion differ with this judgment that the method of fetal death is morally irrelevant to the harvest and therapeutic use of fetal tissue. In their view, abortion is murder, and the transplant surgeon and tissue recipient are somehow accomplices in this immoral act. The policy proposed in this article refuses to take either position concerning the status of the fetus. For the purposes of the policy, the status of the fetus as a person from the time of conception, or simply as part of the pregnant woman's body, is not relevant. No judgment concerning the status of the fetus is necessary, provided there is a clear procedural separation of the use of fetal tissue and the performance of an abortion. As long as an abortion is legal under some circumstances, the use of the fetal tissue from that abortion is justified. As such, the proposal is a pragmatic policy that reflects the support which abortion under some circumstances has among the majority of the American population ("Broad Public Support for Right to Abortion Remains Undiminished, a New Poll Finds; Ambivalence Remains Deep About the Concept," *New York Times*, Jan 21, 1988, p 11).[15,16]

The proposed policy is based on the assumption that the moral and legal status of a fetus and thus the status of the fetus as either intentionally or unintentionally aborted is only one of many issues to be taken under consideration; that is, the moral and legal status of the fetus should not be the determinative principle. This approach involves a complex weighing of moral and cultural values as well as ethical principles within the overall context of fetal tissue harvesting and transplantation.[17] It incorporates guidelines that have been established regarding medical research in other clinical settings. Given that no one principle is determinative of the overall policy, individual components may appear to be in conflict, but the proposed policy needs to be judged as a whole.

In conclusion, in this article I argue for a policy that would allow for the therapeutic use of human fetal tissue from induced abortions, provided that the commercial use or sale of the tissue is prohibited, the designation of the tissue recipient is forbidden, all possible conflicts of interest for a pregnant woman and her physician are eliminated, and informed consent for the use of the fetal tissue is obtained. With such a policy in place, the debate over whether any or all abortions are moral or immoral can proceed apart from the subsequent use of that tissue in therapeutic trials. We should allow the therapeutic use of transplanted human fetal tissue in the treatment of otherwise chronic and unremitting diseases to proceed apart from our societal conflict over abortion.

## REFERENCES


1. Madrazo I, León V, Torres C, et al: Transplantation of fetal substantia nigra and adrenal medulla to the caudate nucleus in two patients with Parkinson's disease (Letter). N Engl J Med 1988; 318:51

2. Hullett DA, Falany JL, Love RB, et al: Human fetal pancreas—A potential source for transplantation. Transplantation 1987; 43:18-22

3. Bakay RAE, Fiandaca MS, Barrow DL, et al: Preliminary report on the use of fetal tissue transplantation to correct MPTP-induced Parkinson-like syndrome in primates. Appl Neurophysiol 1985; 48:358-361

4. Lindvall O, Rehncrona S, Brundin P, et al: Human fetal dopamine neurons grafted into the striatum in two patients with severe Parkinson's disease: A detailed account of methodology and a 6-month follow-up. Arch Neurol 1989; 46:615-631

5. US Department of Health and Human Services: Special Notice: Moratorium on Certain Fetal Tissue Research—NIH Guide for Grants and Contracts, Vol 17. Bethesda, Md, May 9, 1988

6. Annas GJ, Elias S: The politics of transplantation of human fetal tissue. N Engl J Med 1989; 320:1079-1082

7. Lewin DI: Funding ban stalls fetal cell research. J NIH Res 1989; 1:32, 34

8. Greely HT, Hamm TH, Johnson R, et al: The ethical use of human fetal tissue in medicine. N Engl J Med 1989; 320:1093-1096

9. Medical Applications of Fetal Tissue Transplants. Chicago, American Medical Assoc, June 20, 1989

10. Publ L No. 98-507: National Organ Transplant Act of 1984, 42 USC §274e(a)

11. Andrews LB: My body, my property. Hastings Cent Rep 1986; 16:28-38

12. Murray TH: Gifts of the body and the needs of strangers. Hastings Cent Rep 1987; 17:30-38

13. Clark RD, Fletcher J, Petersen G: Conceiving a fetus for bone marrow donation: An ethical problem in prenatal diagnosis. Prenat Diagn 1989; 9:329-334

14. Jonsen AR: Transplantation of fetal tissue: An ethicist's viewpoint. Clin Res 1988; 36:215-219

15. Davis JA: General Social Surveys. Chicago, National Opinion Research Center, 1980

16. Granberg D, Granberg BW: Abortion attitudes, 1965-1980: Trends and determinants. Fam Plann Perspect 1980; 12:250-261

17. Jonsen A, Toulmin S: The Abuse of Casuistry: A History of Moral Reasoning. Berkeley, University of California Press, 1988

# Lessons From the Practice

## The Trivia Champ and Honorary Faculty Member

WILLIAM B. SHORE, MD, *San Francisco*

Mr M was driving the chief resident crazy. Mr M was a 76-year-old patient who called at all times, day or night, complaining about his physical condition and the poor treatment at his board and care facility. Nothing satisfied him. He argued about anything and everything. Once a month, in the middle of the night, he would call an ambulance to take him to the hospital. He would arrive in the emergency department dressed only in his hospital gown, breathing rapidly. Three or four hours later, after costly and time-consuming evaluation, his lab results would come back normal. Even though he was asymptomatic, he was reluctant to return to the board and care home, and so, after all the investment of time, energy, and money, the chief resident would commonly admit him for one to three days. He was driving the chief resident crazy!

When the chief resident was about to leave he approached me, saying that he would not "dare" transfer this impossible patient to another resident and asking if I would take over. Of course I would.

At our first meeting in the clinic Mr M lived up to his reputation. He was unshaven and unkempt, dressed in a dirty hospital gown, demanding treatment, unsatisfied with all my suggestions or options, and, above all, unwilling to accept responsibility for any of his own care. But for all his difficulty, there was something intriguing about this irascible old gentleman.

He had been a bookkeeper. He had never married and had few friends. He had been close only to his father and a pet dog, both of whom had died six years earlier. Following these losses he had become profoundly depressed and was admitted to an inpatient geriatric psychiatric unit. After three months of various therapies, including antidepressant medication, the psychiatric staff thought they had nothing left to offer this man. He was discharged to the board and care facility. When asked, Mr M identified his problems as "ageitis, inertia, and fear of change." He said he feared dying—and living.

In order to better understand Mr M as a patient, I decided to make a home visit to his board and care facility. I found warm and bright common rooms and a spacious sun room. Mr M had a large room, which he had shared with a number of roommates over the years. More than one had died during his stay. The operators of the facility were pleasant and caring but very frustrated with Mr M because he never got dressed or went outside and generally gave them a hard time.

After consultation with our psychologists, I decided on a strategy of intervention. I told Mr M that I would begin making brief weekly visits to him and that my staff team would make telephone calls to him at least three times a week and once on weekends. I told him that, in exchange, he must call us before he called an ambulance to take him to the hospital. I asked the emergency department personnel to call us if he appeared.

Not surprisingly, the first weekend after this plan went into effect, I received a midnight call advising that Mr M was in the emergency department. When I questioned him about this visit, he informed me that he had used a taxi, not an ambulance, to bring him to the hospital. Nonetheless, I clearly restated our agreement—we would call and visit him, but he must call before he came to the hospital. That was his last visit to the emergency department, and he has not been in hospital since.

Within three months the home visits were reduced to one every two weeks, and after six months I visited him monthly. Today, Mr M rarely calls, and we need to call him only infrequently. He maintains the same outward "inertia" as ever and continues to give the board and care operators a difficult time—but he does not want to move because of his fear of change. In our conversations, I continue to be supportive of the staff's efforts to care for him and to set clearly defined limits.

I have come to look forward to my monthly visits with Mr M. He is now 85 years old; he shares the same birthday with my daughter—with a difference of 69 years—and he frequently reminds me of that. He is the Trivial Pursuit® champion of his board and care home and delights in the game.

I have come to see that, to his credit, Mr M has refused to give up the basic parts of himself and his personality that create "difficulties" for people. I have come to recognize these quirks as indices of his strength and will to survive.

This relationship has taught me valuable lessons as a physician and as a teacher. The early home visit gave me a more complete picture of this patient and of his environment. The visit also gave me a reality check against which to gauge his constant complaints about the facility. I learned that putting in time initially may save both time and effort in the long run. I have discussed this approach often with students and residents when they feel frustrated with a particular patient. I have thought at times of making Mr M an honorary member of our faculty in token of just how much he has taught us.

(Shore WB: The trivia champ and honorary faculty member. West J Med 1990 Apr; 152:449)

From the Department of Family and Community Medicine, Family Practice Residency Program, University of California, San Francisco, School of Medicine, and San Francisco General Hospital.

Reprint requests to William B. Shore, MD, Family Practice Residency Program, San Francisco General Hospital, 995 Potrero Ave, Bldg 80, Ward 83, San Francisco, CA 94110.

# Book Reviews

**GRAND ROUNDS—ONE HUNDRED YEARS OF INTERNAL MEDICINE**—Edited by Russell C. Maulitz, Staff Physician, Presbyterian—University of Pennsylvania Medical Center, and Lecturer in History and Sociology of Science in Medicine, University of Pennsylvania School of Medicine, and Diana E. Long, Director of the Francis C. Wood Institute of the College of Physicians and Adjunct Associate Professor, University of Pennsylvania, Philadelphia. University of Pennsylvania Press, Bockley Hall, 13th Floor, 418 Service Dr, Philadelphia, PA 19104, 1988. 367 pages, $34.95.

This volume is a compilation of conference papers generated in March 1986 for the second national conference at the Francis C. Wood Institute for the History of Medicine. Established in 1978, the Wood Institute of the Philadelphia College of Physicians held its first annual conference on the history of the American general hospital in 1984. This work honors Francis C. Wood and provides a scholarly chronicle and analysis of the emergence of internal medicine as a professional specialty during the past century.

According to Institute director and editor Diana E. Long, Wood's own professional life reflected the "remarkable transformation of American medicine" from the second decade of the 20th century to the present. Wood was a pathbreaker in the development of the subspecialty of cardiology. His career provides the model for the other subspecialties explicated in this text. He published over 50 papers encompassing numerous aspects of cardiovascular problems and assumed leadership of the elite medical scientific societies. World War II was a central event in the vast expansion of the American medical and scientific establishment. As Chief of Medicine at the 20th General Hospital in Assam, India, where the mortality rate was less than 1%, Wood's activities paralleled this expansion. In the postwar era he was an organizational leader who seized the opportunity of the enormous infusion of federal funds and emergence of large-scale institutions to enlarge activities in his own medical community.

Building on the Wood profile, the contributors to *Grand Rounds* describe aspects of the professionalization and specialization of internal medicine and five of its eleven subspecialties. Three introductory chapters by Russell C. Maulitz, Maulitz and Paul B. Beeson, and W. Bruce Fye, set forth the larger interpretive framework for the five subspecialty case studies that form the core of the collection.

In "The Inner History of Internal Medicine," Maulitz and Beeson assess its strengths and weaknesses as a specialty. They review benchmarks in its development with a focus on the post-World War II period. After 1950 and the great leap in research funding, the specialty fractured into a wide plurality of subspecialties. They argue that the explosion of knowledge and geometric growth of the subspecialty rendered it without clear boundaries and definition. Ironically, however, this structural ambiguity had positive social benefit. Internal medicine's broad contours have enabled it to transcend the narrow focus of other specialties organized around a particular organ system and technology. Its practitioners view human health and disease from a holistic perspective and better apply the principles of comprehensive care.

Cardiology formally became a subspecialty of internal medicine in 1940, when the new American Board of Internal Medicine voted certification of internists in allergy, gastroenterology, and both pulmonary and cardiovascular disease. Joel D. Howell's "Heart and Minds: The Invention and Transformation of American Cardiology" is a particularly compelling case study of this process for the historian because the author provides a rich historical context for the formative medical events.

The four other case studies only occasionally miss the high stylistic mark of Howell's narrative. Edward H. Kass discusses infectious diseases, Joseph B. Kirsner explores gastroenterology, Thomas G. Benedek reviews a century of rheumatology, and Steven J. Peitzman assesses developments in nephrology from Thomas Addis to the artificial kidney. At times a rigid structure in these chapters, perhaps imposed by the editors, tends to inhibit the natural flow of discussion into a stilted chronicle of professional literature and associationalism. Nevertheless, the publication is an important interdisciplinary contribution to the history of medicine and an effective means of disseminating the vital gathering of knowledge in academic centers for historical studies in the health sciences.

Rosemary Stevens concludes the collection with a succinct elaboration of the themes introduced by Maulitz and Beeson. She pinpoints the central paradox of internal medicine as a specialty. Because of its ambiguous definition and fragmentation into so many major subspecialties, it exists only because its practitioners are organized into highly regarded professional societies and publish professional journals. Ironically, this very ambiguity is also the specialty's greatest strength. By the middle 1980s, about a fourth of all United States resident physicians were in approved internal medicine programs, and the American Board of Internal Medicine granted almost 40% of all primary specialty certificates. Internal medicine has become a "self-defined conscience for medicine"; its practitioners view the human body as a whole and as an interactive part of its physical environment.

RICKEY HENDRICKS, PhD
*Department of the History of Health Sciences*
*University of California, San Francisco*

* * *

**DIAGNOSTIC NUCLEAR MEDICINE—Second Edition—2 volumes**—Edited by Alexander Gottschalk, MD, Professor and Chairman, and Paul B. Hoffer, MD, Professor and Chief of Nuclear Medicine, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut, and E. James Potchen, MD, Chairman, Department of Radiology, Michigan State University, East Lansing. Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202, 1988. 1,154 pages, $215.

This very well-organized two volume reference work (formerly known as *Golden's Diagnostic Radiology*) reappears on the nuclear medicine literature scene in timely fashion. After a short plateau, this field is again blossoming rapidly, and a well-produced compendium of this nature is welcome. As with all textbooks in dynamic fields, some of the latest coverage is, of necessity, curtailed, but even that slight shortcoming is minimal.

There are 75 chapters in 17 sections that cover a broad scope, including the history of the discipline, physics and instrumentation, radiation protection and dosimetry, radiopharmaceuticals, and methods of data interpretation. There are 125 contributors, well-known in the field. The broad spectrum of areas amenable to radionuclide investigation and therapy is showcased in this work. In addition to the more common areas of heart, lung, bone, renal, and oncologic disease, the volumes cover well those of hematology, gastroenterology, vascular studies, endocrinology, pediatrics, infection, and trauma. Indeed, sections on radioimmunoassay and radioactive iodine therapy are excellent updates. Neurology, a field for years relinquished to the province of computerized tomography and magnetic resonance imaging, has been more recently reopened to nuclear medicine, and this new information is included.

The text is well-written and avoids some of the hyperbole and convolution frequently found in ambitious survey textbooks. The illustrations are good, and the index is as adequate as can be expected in this type of work, with references dating even up to a year before publication. As another reviewer has suggested, the color plates for cardiology and neurology studies could perhaps have been placed other than at the beginning of the book with the table of contents, but considering the stature of the editors, this too was probably the result of careful consideration. Very little is omitted, although one might expect even seldom employed techniques such as salivary gland imaging to be included in a comprehensive textbook. Printing errors are virtually nonexistent.

In summary, this two-volume textbook deserves a place in the library of any physician or facility involved in the practice of nuclear medicine. It is of the highest quality and certainly sets a new standard for a complete reference source in this field.

DAVID B. HERTSGAARD, MD
*Director, Nuclear Medicine*
*Saint Joseph Hospital and*
*Childrens Hospital of Orange County*
*Orange, California*

# INFORMATION FOR AUTHORS

## Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, PO Box 7602, San Francisco, California 94120-7602. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976*, transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar, and spelling.

### *Clinical Investigation Section*

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

## Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables, and references) on one side of the paper, with 1½-inch margins. Articles should not exceed 3,000 words (less than 15 text pages typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

### *Style*

*Abbreviations.* Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

*Weights and measures.* Use Système International (SI) units throughout the manuscript. Provide metric equivalents for all SI units; they will be noted parenthetically in the published text.

*Temperatures.* Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

*Drug names.* If the trade name of a drug is used, the generic name, including salt or ester, should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

### *Title Page*

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses, and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

### *Abstract*

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented," or "was investigated."

## Tables and Figures

### *Tables*

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title, and have its position indicated in the text.

### *Illustrations (Figures)*

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and the position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

### *Legends*

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

### *Permission for Reproduction*

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

## References

References should be limited to those cited in the text and should be to medical, scientific, or scholarly publications. (Mass circulation periodicals are referenced in parentheses in the text.) They must be typed double-spaced and numbered consecutively as they appear in the manuscript.* (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

### *Journal Articles*

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, use of inclusive page numbers, and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

### *Books*

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

### *Pamphlets, Monographs, or Books With No Given Author*

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

### *Articles in Press or Accepted for Publication*

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear and the phrase "in press" or "accepted for publication" in place of the date of publication.

### *Personal Communications and Unpublished Data*

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was oral or written, and the person's name, highest academic degree, and professional affiliation should be provided.

---

**Exception:* Articles for Topics in Primary Care and Epitomes use a limited number of authoritative references, both to the specific topic and the subject as a whole, that are *not* cited in the text and are listed in alphabetic order.

## Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

## Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians, or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects, and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

## Author Responsibility

Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously, and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

## Reprints

If reprints are desired, they must be paid for by the author. A reprint order form with schedule of prices is sent to the author when the article is published. Authors are responsible for handling requests for reprints of their articles.

Revised 10/1/87

# COMING IN THE MAY ISSUE

## Addiction Medicine
### and the Primary Care Physician

Special Editor David E. Smith, MD, Founder and Director of the Haight Ashbury Free Clinic in San Francisco, and a distinguished group of addiction medicine specialists will discuss the disease concept of addiction, drug testing in the workplace, addiction and special populations—the adolescent, patients with dual diagnoses, persons with the acquired immunodeficiency syndrome and chemical dependency, pregnant addicts, the drug-exposed neonate, the impaired physician—and many other topics.

Each year THE WESTERN JOURNAL OF MEDICINE features a single-topic issue on a timely subject of interest to its readers. ADDICTION MEDICINE AND THE PRIMARY CARE PHYSICIAN presents a practical and pertinent discussion of a problem that affects the lives of all health care professionals. Look for it in May.

# Classified Advertisements

The rate for each insertion is **$7 per line** (average six words per line) **with five line ($35) minimum.** Confidential box number charge: $5 each month.

**Classified display rates $50 per inch. Maximum sizes: 1 column by 10 inches or 2 columns by 5 inches. Larger classified ad space by special arrangements.**

Copy for classified advertisements should be received not later than **25th of the second month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. Although The Western Journal of Medicine believes the classified advertisements in these columns to be from reputable sources, we do not investigate the offers made and assume no liability concerning them. The right is reserved to reject, withdraw, or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

**Please Type or Print Advertising Copy**

## Classified Advertisements Are Payable in Advance

CLASSIFIED ADVERTISEMENTS
THE WESTERN JOURNAL OF MEDICINE
P.O. BOX 7602, SAN FRANCISCO, CA 94120-7602
(415) 541-0900, ext. 376

## PHYSICIANS WANTED

### CALIFORNIA

Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Carol Sweig or Jim Ellis, Directors, (415) 673-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (818) 999-1050 or (800) 635-3175.**

**SAN FRANCISCO BAY AREA.** Full-time career Emergency Physician wanted for a high volume Emergency Department, 30 minutes south of San Francisco. Emergency Medicine BC/BE mandatory; prefer experienced. Congenial, democratic group of 20 full-time physicians doing some follow-up and minimal overnights. Competitive salary with excellent benefits including three to five weeks paid vacation; seven paid holidays; malpractice, medical, dental, and disability insurance; corporate shareholder in three years. Send CV or contact Drew Baker, MD, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545; (415) 784-4521.

**INTERNAL MEDICINE.** Long established multispecialty group in central Washington needs Internist. Independent contract or join partnership later. University town with many cultural and recreational activities. Send CV to Medical Building Associates, 200 E. 6th, Ellensburg, WA 98926, or call (509) 925-9891.

**GYNECOLOGIST** needed for 78-bed JCAHO hospital. We are growing and we need to enlarge our specialty staff. Just opened new Cancer Treatment Center. 12,000 community, 90,000 immediate service area, 160,000 catchment area. Great outdoors area, cattle, oil, gas, hunting, fishing, good schools, low crime, ideal area for raising children. Reasonable malpractice rates. Send CV to Marilyn Bryan, Community Hospital, PO Box 2339, Elk City, OK 73648; (405) 225-2511.

**SAN FRANCISCO AREA.** Family Practitioner or Primary Care Internist to join progressive six physician group in lovely coastside community of Half Moon Bay, 25 miles south of San Francisco. CV to Dr Larry Casalino, 225 S. Cabrillo Hwy, Half Moon Bay, CA 94019.

### Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services,
5414 E. Montecito, Fresno, CA 93727.
Or call 1 (800) 873-0786.

**PHYSICIAN OPPORTUNITIES IN ARIZONA.** Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 90 plus physicians in Tucson, Green Valley, and Tempe, Arizona, has positions available in these cities in Internal Medicine, Pediatrics, OB/GYN, Orthopedics, Urgent Care, and Family Practice. Excellent fringe benefits and profit sharing program. Fee-for-service, as well as owned HMO. Must be BE/BC. Call or write James J. Vitali, CEO, Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732; (602) 322-8300.

**NEAR STANFORD.** Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

**CALIFORNIA—NORTHERN.** Area's leading private practice group has immediate and future positions for BC/BE Family Practice and Primary Care Physicians in its Department of Ambulatory Care and General Medicine. Excellent compensation, incentive program, full benefits, early equity position, retirement plan. Experience lifestyle and professional fulfillment in beautiful northern California. Call Maureen Forrester: (408) 282-7833. Send CV to San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112.

**PHYSICIAN OPENING.** Ambulatory care/minor emergency center. Full/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

*Join the leader* *and enjoy your practice!*

### Family Practice

Pacific Physician Services
A dynamic and growing 65-physician Southern California medical group network, has immediate career opportunities for primary care physicians. Examine our benefits:

- $8K monthly guarantee;
- Monthly FFS productivity incentives;
- Paid malpractice;
- Medical & dental plans;
- Retirement, disability;
- Vacation, CME, sick time.

Discover an enjoyable practice, call

**Ruthan Smith**
**(800) 338-4798**
**or (714) 825-4401 in CA**

**OB/GYN, INTERNISTS,** Family Practitioners, Pediatricians for Arizona and western opportunities. Quality positions available other regions of country. Inquiries confidential. Mitchell & Associates, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

**INTERNAL MEDICINE, NORTHERN CALIFORNIA.** You have a unique opportunity to join the area's leading multispecialty private medical practice. A position is available immediately for a BE/BC Internist. All subspecialties welcome to apply. Generous salary, bonus provision, fringe benefit package, and early membership in the corporation. Accept the challenge; become part of our competitive, growing organization. Experience the good life—wonderful restaurants, beautiful scenery, great weather, cultural facilities, easy access to beaches and mountains. Send CV and receive further information by contacting Maureen Forrester, Physician Recruitment, 45 S. 17th St, San Jose, CA 95112; (408) 282-7833, (408) 282-7757.

**FAMILY PRACTITIONER, NORTHERN CALIFORNIA.** Solo Family Practitioner (including OB) seeks BE/BC associate. English/Spanish preferred. Reasonable call. Beautiful "Redwood Empire" town, two hours from San Francisco. Guaranteed salary, benefits. Contact Andrew Coren, MD, 1165 S. Dora, E2, Ukiah, CA 95482; (707) 463-3663.

**SOUTHERN CALIFORNIA.** 39,000 visit Emergency Department in new hospital in San Bernardino. Base station and separate fast track with opportunity to teach. Opening for director and career Emergency Physicians at $90 per hour. Chance to join prestigious, democratic, academically oriented emergency group with excellent benefits. Contact Art Wong, MD, FACEP. Emergency Physicians Medical Group, 120 Montgomery St, San Francisco, CA 94104; (415) 989-1242.

*(Continued on Page 454)*

(Continued from Page 453)

PHYSICIANS WANTED

## CALIFORNIA, ARIZONA OR UTAH YOUR CHOICE

There are private practice opportunities now available in the following Humana California, Arizona and Utah communities

LOS ANGELES CO., CA

ORTHOPEDIC SURGEON—A young Orthopedic Surgeon practicing in the San Fernando Valley for the past five years is seeking an associate. Also, a well-established two man group is now seeking a third member with a Spine Fellowship.

PHOENIX

OB/GYN—Two young, boarded, solo OB/GYN's with thriving practices are each seeking an associate in suburban Paradise Valley.

LAYTON, UTAH

FAMILY PHYSICIANS—Associate needed to join young, board-certified Family Physician in newly opened office. Layton is 12 miles south of Ogden and 15 miles north of Salt Lake City.

For further information, send your CV to: Gordon Crawford, Manager, Professional Relations, Humana Inc., Dept. HH-4, 500 West Main Street, Louisville, KY 40201-1438. Or call TOLL-FREE 1-800-626-1590.

**Humana®**

**RADIOLOGIST.** Part-time position available immediately in small hospital with general radiography and fluoroscopy, mammography and ultrasound in Weaverville, California. Contact Drs Wheeler, Biggs, or Babbitt, West Coast Radiology, 3798 Janes Rd, Ste 12, Arcata, CA 95521; office number (707) 822-3621, ext 191.

**SAN FRANCISCO NORTH BAY AREA/NAPA VALLEY.** Immediate openings (career and part-time) in a multidiscipline Emergency Department for physicians trained in Emergency Medicine, Internal Medicine, Family Practice, or Pediatrics. Full in-house multispecialty coverage. Complete generous benefit package. Contact Robert Mack, MD, Kaiser Hospital, 975 Sereno Dr, Vallejo, CA 94589; (707) 648-6200. EOE.

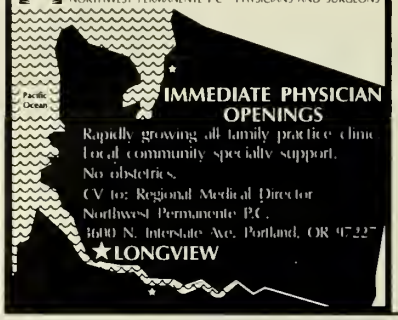
**CALIFORNIA, NORTHERN.** A stable group of four ABEM certified/eligible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klammath, Rogue, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1000, San Francisco, CA 94104.

**SEEKING A PHYSICIAN** to associate with a Family Practice group. Ultramodern facility with outpatient surgical suite. Located in Corona, California, between Orange County and San Diego. Growing area. Good climate. We are offering an association with excellent economic advantage. Contact Ann Holmes, (714) 734-3042.

PHYSICIANS WANTED

## LONGVIEW, WASHINGTON

KAISER PERMANENTE
NORTHWEST PERMANENTE P.C. PHYSICIANS AND SURGEONS




Longview is a picturesque, stable community of 42,000 located near the Columbia Gorge and the coastal mountains and beaches of Washington and Oregon. Members of our 12 physician group enjoy individual subpractices, infrequent call, and excellent facilities in our new clinic. We invite you to contact us regarding practice opportunities.

**WASHINGTON.** BC/BE General Internists to join expanding 32 physician multispecialty group located in the foothills of the Blue Mountains. Excellent schools, cultural, and recreational opportunities. One junior college and two four-year colleges are located in the community. Guaranteed income with excellent benefit program. Send CV to Connie Goude, 55 W. Tietan, Walla Walla, WA 99362.

**SAN JOSE, CALIFORNIA.** Urgent Care. Positions currently available for experienced physicians to provide primary care services at hospital based Urgent Care Center in San Jose. Minimum guarantee of $100,000 plus annual for 42 hour work week with one month vacation and paid malpractice. No night call. Please contact Nanette Peter at AEP, (408) 293-8881.

**NORTHERN CALIFORNIA.** The Permanente Medical Group, Inc, has immediate openings for BC/BE General Internists at the Roseville facility. Kaiser Permanente is a leader in health care, providing quality medical care to a rapidly growing population. We offer a tremendous benefit package and starting salary for career oriented physicians. Roseville is a foothill community located 90 miles from San Francisco and 100 miles from Lake Tahoe and Sierra skiing. University affiliation and teaching appointments are available. Send CV to Tony Cantelmi, MD, The Permanente Medical Group, Inc, 1001 Riverside Blvd, Roseville, CA 95678. EOE.

**CALIFORNIA.** Fellowship in Ambulatory Pediatrics available January, 1990. Active clinical service in major medical teaching center with over 70,000 outpatient visits per year. Opportunity for clinical, teaching, administration, and research training. Contact Laura Wachsman, MD, LAC/USC Medical Center, Pediatric Pavilion, 1129 N. State St, Rm 1D37, Los Angeles, CA 90033; (213) 226-3624.

**CALIFORNIA.** Seeking BE/BC Pediatricians to staff busy inner city Pediatric emergency room in major teaching center with over 40,000 visits per year. Opportunities for flexible scheduling and various shifts. Full-time or part-time. Contact Dee Hodge III, MD, Dept of Pediatrics, LAC/USC Medical Center, 1129 N. State St, Rm 1D37, Los Angeles, CA 90033; (213) 226-3632.

**AMBULATORY CARE.** Full-time/part-time openings, northern, southern, and central locations. Competitive salary, strong incentive package, and growth potential. Malpractice paid. Join our partnership of established Emergency Medicine and Ambulatory Care Physicians. Contact Jane Dressler, California Emergency Physicians, 2101 Webster St, Ste 1050, Oakland, CA 94612-3027; (415) 835-7431 or (800) 842-2619.

**MULTIPLE FAMILY PRACTICE** (BC/BE) positions available in several suburban satellite clinics of a large Seattle area multispecialty group practice. Diverse patient population includes managed care, fee-for-service, and retired military (at some satellite clinics). Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

## SOUTHERN CALIFORNIA

Specialists and Primary Care Physicians—CIGNA Healthplans invites you to join our innovative and dynamic managed health care team. Our multidisciplinary HMO practice provides a supportive and collegial work environment at 31 locations. You will enjoy a wealth of cultural and recreational activities, access to major academic centers, and an excellent compensation package. *Call collect* **(818) 500-6570** *or send CV to* **Robert Harrington, MD, Professional Recruitment, CIGNA Healthplans of California, 505 N. Brand Blvd, Ste 400-49, Glendale, CA 91203.**

**GERIATRIC MEDICINE.** Unique practice opportunity in hospital-based comprehensive geriatric care center. Patient care with excellent opportunities for teaching and research. Guaranteed income. Reply with CV to Alan Lazaroff, MD, Senior Citizen's Health Center, 601 E. 19th Ave, Denver, CO 80203; (303) 869-2269.

**CALIFORNIA LICENSED BC RADIOLOGIST** for back-up locum tenens, plus potential full-time. Contact I.V. Radiology Medical Group, 1266 Pepper Dr, El Centro, CA 92243; (619) 352-5666 after 6 pm.

**SAN FRANCISCO PENINSULA.** Well trained BC Internal Medicine, Family Practice, or Emergency Room MD for busy Urgent Care Division of large, private, multispecialty group practice. Full-time position. Send CV to S. M. Stone, MD, Palo Alto Medical Foundation, 300 Homer Ave, Palo Alto, CA 94301.

**GENERAL INTERNIST.** Multispecialty group located in San Luis Obispo, California, seeks a BC/BE physician. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to Physicians Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

**FAMILY PRACTITIONER.** Multispecialty group located in San Luis Obispo, California, seeks a BC/BE physician. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to Physicians Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

**BC/BE INTERNIST NEEDED.** Opportunity to join part of a comprehensive medical group practice located in the suburbs of San Francisco. Professional setting of 36 physicians. Forward CV to Peter Earley, Physician Relations, Ross Valley Medical Group, 2200 Larkspur Landing Circle, Ste 103, Larkspur, CA 94939.

**OB/GYN. MD BE/BC NEEDED** in northern California. Opportunity to join part of a comprehensive medical group practice. Professional setting of 36 physicians. Beautiful suburb of San Francisco. Forward CV to Peter Earley, Physician Relations, Ross Valley Medical Group, 2200 Larkspur Landing Circle, Ste 103, Larkspur, CA 94939.

(Continued on Page 455)

(Continued from Page 454)

PHYSICIANS WANTED

# Join us.

**PACIFIC NORTHWEST**
**Group Health Cooperative of Puget Sound**

One of the nation's largest and oldest HMOs currently has permanent and locum tenens positions available for:

Family Practitioners
Pediatricians
Physician Assistants
Psychiatrist–General
Psychiatrist–Child
Psychologist

To inquire, write:
Manager, Medical Staff Personnel
Group Health Cooperative of Puget Sound
521 Wall Street
Seattle, WA 98121

or call (206) 448-6546

# PHYSICIANS

## PRIMARY CARE

## CALIFORNIA

JSA, Inc. is currently offering physicians full, part-time, and PRN positions in Primary Care Clinics located in San Diego and Sacramento.

### BENEFITS PACKAGE

- **Flexible day-time hours**
- **No "on-call" requirement**
- **Malpractice insurance reimbursement**
- **Professional development funding**
- **Incentive programs**
- **Exceptional salary level**

### QUALIFICATIONS

- **BC or graduate of an approved residency program in a Primary Care Specialty**
- **MD or DO**
- **Current state licensure**
- **ACLS/BCLS**

A proposed project in Oceanside includes positions in Emergency Medicine and Primary Care Specialties.

For further information, please contact Susan Bray, Recruiting Director at (301) 964-2811. JSA, Inc., PO Box 1305, Columbia, MD 21044.

HEALTHCARE
Consulting - Management - Services

An Equal Opportunity Employer

(Continued on Page 456)

# THE PERMANENTE MEDICAL GROUP
# NORTHERN CALIFORNIA

QUALITY

STABILITY

LEADERSHIP

GROWTH

SUPPORT

REWARDS

The Permanente Medical Group, the largest multispecialty group practice in the U.S., is undergoing explosive growth in its Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley. Our rapid increase in membership has created practice opportunities throughout the region.

Our physician-managed group is part of the comprehensive Kaiser Permanente Medical Care Program. As a TPMG physician, you have access to the latest medical technology and resources, the support of colleagues in all subspecialties — and the opportunity to provide excellent health care without the burdens of managing a practice.

TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, continuing education, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. For complete information, call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-7153, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800) 777-4912. EOE

KAISER PERMANENTE
*Good People. Good Medicine.*

(Continued from Page 455)

PHYSICIANS WANTED

# WASHINGTON STATE
## ROCKWOOD CLINIC, PS

An expanding 65 physician multispecialty fee-for-service group seeks BC/BE physicians in the following specialties:

ALLERGY
CARDIOLOGY
DERMATOLOGY
INTERNAL MEDICINE
PEDIATRICS
FAMILY PRACTICE—permanent, part-time, locum tenens
GASTROENTEROLOGY
HEMATOLOGY/ONCOLOGY
OB/GYN
RHEUMATOLOGY
GENERAL SURGERY
ORTHOPEDICS

Attractive benefit package includes competitive salary leading to early shareholder status.

CONTACT: **Colleen Mooney, Recruitment Coordinator**
**Rockwood Clinic, PS**
**E. 400 Fifth Ave**
**Spokane, WA 99202**
**(509) 838-2531**

**COME ENJOY SPOKANE'S QUALITY LIFE-STYLE!**

**PSYCHIATRIST FOR ROCKY MOUNTAIN CITY.** An impressive Rocky Mountain community in Montana seeks psychiatrist for well managed mental health clinic. Opportunity to succeed the present medical director exists within the next two to three years. Position includes both patient care and program development. Community population is over 80,000 with two modern hospitals. Liberal financial package offered. For more information call Gwyneth Anderson, (800) 221-4762, or write to E. G. Todd Associates, 535 Fifth Ave, Ste 1100, New York, 10017.

**PUGET SOUND.** BC/BE Family Practitioner for new branch office of multispecialty clinic. Full Family Practice opportunity, OB optional. Guaranteed starting salary and benefits. Respond with CV to Memorial Clinic, Attention: Inge Hart, Personnel, 500 N. Lilly Rd, Olympia, WA 98506; (206) 456-1122, ext 249.

**TUCSON, ARIZONA.** BC/BE, residency trained Family Physician sought to join busy solo Family Physician in private practice. Attractive start-up package available. Send CV to Herb Jalowsky, MD, 1925 W. Orange Grove Rd, Tucson, AZ 85704; (602) 622-1414.

## OB/GYN
## CALIFORNIA'S NORTH COAST

Exceptional opportunity to have a quality, thriving solo or partnership practice with coverage. There is a real need for an additional OB/GYN to establish a practice to keep pace with the expansion of our well equipped/full-service hospital, including the doubling of our OB department and referral base. University community on the beautiful redwood coast has superb educational, cultural, and recreational activities. Adjacent office space is available. BE/BC physicians should call and/or send CV to:

**Physicians Recruitment Committee**
**Mad River Community Hospital**
**PO Box 1115**
**Arcata, CA 95521**
**(707) 822-3621, ext 263**

**CENTRAL CALIFORNIA.** Join our team of Family Practice Physicians in a progressive community health center near Fresno, California. Competitive salary with extra on-call and overtime. Malpractice paid. Generous vacations and time-off policy. Affiliated with UCSF with on-site Family Practice residents and medical students. Varied practice, including Obstetrics, Pediatrics, and in-patient care with an emphasis on health maintenance, patient education, and primary care research. Position is 60 percent clinical, 40 percent teaching. Bilingual English-Spanish helpful. Contact Ardeth Bier, Fresno County Dept of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3353.

**ARIZONA.** Established Emergency Medicine group has immediate openings for full- or part-time BC/BE physicians seeking career opportunity in busy Emergency Department with excellent location and case mix. Flexible schedules, excellent living and working conditions. Compensation range $150K to $200K for full-time. Send CV in confidence to General Manager, PO Box 80412, Phoenix, AZ 85060-0412.

**URGENT CARE PHYSICIAN.** Full- or part-time position available for northern California urgent care clinic. Contact David Lyons, MD, 900 Oro Dam Blvd, Oroville, CA 95991; (916) 534-9183.

**INTERNIST FOR NEBRASKA.** A growing regional medical center in Nebraska seeks an Internist to complement a group of highly qualified peers. Modern, progressive hospital will purchase equipment as needed. Competitive compensation package includes malpractice. Regional community for recreation, culture, and shopping. Call Gwyneth Anderson at (800) 221-4762. E. G. Todd Associates, 535 Fifth Ave, Ste 1100, New York, NY 10017.

**MD TO ASSIST** in busy Orthopedic clinic and Operating Room. Will also take call. Position has been used in the past as a bridge to orthopedic residency. Attractive salary and excellent benefit package. Washington State licensure required. Available immediately. Send CV or contact Mary Anderson, Personnel Representative, Pacific Medical Center, 1200-12th Ave S., Seattle, WA 98144; (206) 326-4111.

PHYSICIANS WANTED

## PHYSICIANS NEEDED

The continuing growth of our service area population (now 90,000) has created an immediate need for additional BC/BE physicians in the following specialties:

- **FAMILY PRACTICE.** Several openings offering a variety of practice situations, above average income potential.
- **ONCOLOGY.** Establish private practice with no investment, guaranteed income. Some General Internal Medicine necessary initially.
- **GENERAL SURGERY.** Exceptional opportunity to assume excellent private practice. Guaranteed income.
- **ORTHOPEDIC SURGERY.** Guaranteed income, established office. Above average income potential.
- **EMERGENCY MEDICINE.** Hospital position, BC/BE in Emergency Medicine, or equivalent combination of appropriate residency training and Emergency Medicine experience. California license required. Competitive remuneration, paid malpractice insurance, individual contract, flexible scheduling, CE allowance. Part-time for double coverage also available.
- **RADIOLOGY.** Hospital group position. Excellent salary and benefit package. Competency in ultrasound, CAT, Nuclear Medicine, film screen mammography, and general diagnosis required. MRI experience desired. Inpatient and outpatient.

112-bed full service, acute care hospital, excellent ancillary services. California license required. Located in central California near Sequoia National Park, Tulare offers a family oriented environment, abundant and varied recreation, good schools, restaurants, and shopping. Beautiful, affordable homes close to hospital and office. Strong economy. New businesses are contributing to the steady growth of our active community which combines the life-style advantages of a small city with easy access to all California attractions.

Contact:
**Tulare District Hospital**
**Physician Recruiting**
**Office, PO Box 90112,**
**Los Angeles, CA 90009;**
**(213) 216-2687.**

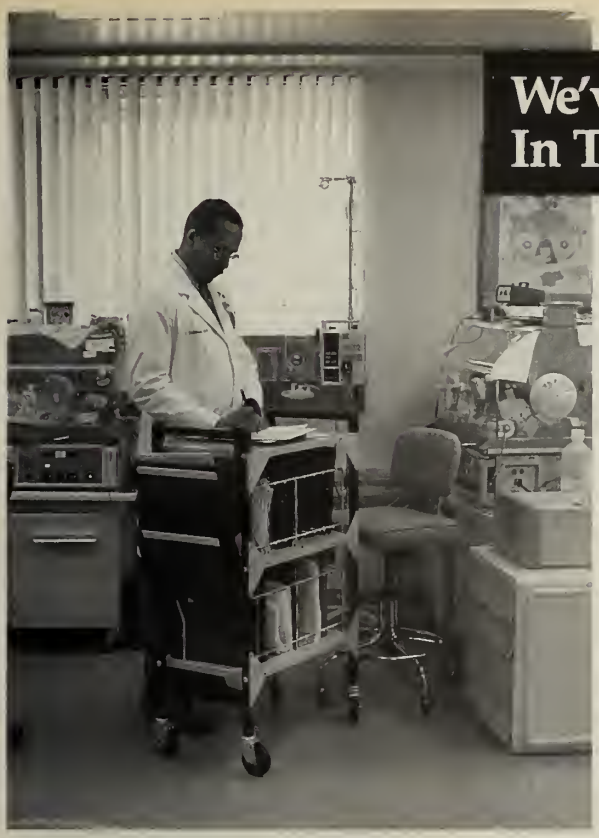
**ACADEMIC CLINICAL HEMATOLOGIST.** The Department of Medicine and the Hematology/Oncology Division of the University of California Medical Center, San Francisco is seeking an experienced Hematologist for a full-time academic position at the level of Assistant Professor. The applicant is expected to have conducted clinical research in acute leukemia. Major responsibilities will include teaching in a large fellowship training program and conducting clinical research in the Cancer Research Institute. Experience with bone marrow transplantation is highly desirable to fit in with an active program currently in place. Correspondence should be directed to Marc A. Shuman, MD, University of California Medical Center, Cancer Research Institute, Box 0128, San Francisco, CA 94143. UCSF is an Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.

**OB/GYN.** Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

**PHYSICIAN OPPORTUNITIES NATIONWIDE**

For all specialties for hospitals, clinics, multispecialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists, **Nugent & Grant, Inc, 1400 Coleman, Ste B-22, Santa Clara, CA 95050; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

(Continued on Page 457)



# We've Put Life-Saving Technology In The Right Hands.

At FHP, providing quality health care is our number one priority. Because this commitment is so vital to us, we've put this challenging responsibility in the most capable hands around. Then we make sure they have everything they need to perform at their highest level.

As one of our valued Physicians, you'll experience all the benefits that come from working with one of the nation's largest and most progressive HMOs. You'll work with dedicated colleagues in every discipline with a wide range of advanced health care equipment at your disposal. Perhaps the greatest benefit is the professional freedom you'll enjoy.

We've alleviated many of the headaches of private practice while providing a predictable work schedule and fully-paid malpractice insurance.

This new found freedom will give you more time to enjoy all the benefits of our attractive locations in Southern California, Arizona, New Mexico, Utah and Guam. No matter what your personal desires, FHP has a location to satisfy them.

Get your hands on a rewarding career with FHP. Call us toll free at 800-336-2255 (in CA) or 800-446-2255 (outside CA). Or send your CV/resume to: FHP, Professional Staffing, Dept. 99, 9900 Talbert Avenue, Fountain Valley, CA 92708. Equal Opportunity Employer.

A graduate of Washington University and the New Jersey School of Medicine, Neonatologist Eugene L. Mahmoud, M.D., joined FHP in July of 1989. Dr. Mahmoud completed his fellowship at the University of California at San Diego in Neonatology and is currently on staff at FHP Hospital's Level II NICU unit.

Giving Physicians More Of What They Want

FHP® HEALTH CARE


*(Continued from Page 456)*

**CALIFORNIA, SANTA CLARA COUNTY.** Positions currently available for experienced physicians to provide primary care services at hospital based Urgent Care Center in San Jose. Minimum guarantee of $100,000 plus annual for 42-hour work week, 48 weeks per year with paid malpractice. No night call. Please contact Nanette Peter, Associated Emergency Physicians, Inc, Medical Group of Northern California, 1625 The Alameda, Ste 201, San Jose, CA 95126; (408) 293-8881.

**ALBUQUERQUE, NEW MEXICO.** BC/BE Family Practitioners sought to join established, private practice, single specialty group practice. Income guarantee, benefits. Please send CV to Kathryn Rhoades, Presbyterian Healthcare Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 6330.

**BC/BE INTERNAL MEDICINE** physician for Primary Care group practice in growing Fresno Community. Well orchestrated/staffed office with associated lab. Contact Michael W. Lynch, MD, 5151 N. Palm, Ste 200, Fresno, CA 93704; (209) 229-2786.

**BC/BE NORTHWESTERN CALIFORNIA.** OB/GYN needed to join the oldest office in the Redwood area on the North Coast. An excellent opportunity for a male or female, American trained physician. Excellent compensation and incentive program leading to corporate membership in one year. Three physicians in office but only two doing Obstetrics. Send CV and references to T. W. Loring, MD or W. C. Weiderman, MD, 2607 Harris St, Eureka, CA 95501; (707) 442-4593.

**SAN FRANCISCO BAY AREA** multispecialty group seeks Pediatrician BC/BE, to join 26 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Daniel Rowe, MD, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

**HAWAII.** Family Practitioner needed for rural underserved area. Full-time position in nonprofit community health clinic. No OB, hospitalizations optional. Desire dedicated person to work in multicultural setting. Contact Alan Chun, MD, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-7081.

**CALIFORNIA MULTISPECIALTY.** Cardiologist, Internal Medicine, Pediatrician, Endocrinologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center, 17821 S. Pioneer Blvd, Artesia, CA 90701.

## OCCUPATIONAL/INDUSTRIAL MEDICINE

Rare opportunity for physician—BC in Occupational Medicine—to join **LARGE,** well established Industrial Medicine practice. Seeking dynamic, motivated individual possessing strong clinical skills. Ideal candidate would also enjoy interfacing with employers, insurance companies, and other members of the safety and health care team. Excellent income potential and benefits. Please reply to:

**Carol Hewes, Director**
**1800 Westwind Dr, Ste 401**
**Bakersfield, CA 93301**
**(805) 324-8811**

**NORTHERN AND SOUTHERN CALIFORNIA OPPORTUNITIES.** We are retained by several hospitals and group practices as far north as the Oregon border, within one hour of San Francisco, Los Angeles, and major central valley cities including Bakersfield and Fresno, and as far south as San Bernardino. Our clients offer outstanding solo, group, hospital based, and HMO practices. Positions are salaried and/or fee-for-service. Typical offers include benefits, CME, and moving expenses. Current needs are for BC/BE Family Practice, Pediatrics, Internal Medicine (all subspecialties), Cardiology, OB/GYN, Orthopedic Surgery, ENT, Urology, and Neurology. Call or send CV to Ken Baker, The Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

**PEDIATRICIAN BC/BE** needed to join four physician department in busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 198, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**INTERNIST,** Pediatrician to join multispecialty group. Salary with incentive, early partnership. Northern California. Reply to Number 197, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**OB/GYN.** Growing well established (1945) multispecialty medical group seeks BE/BC OB/GYN. First year salary, insurance, vacations, and coverage. Second year shareholdership and partnership. Five miles southeast of downtown Los Angeles. Practice in fully equipped building. Hospital nearby. Send CV in confidence to Craig Kaner, All Care Medical Group, 2675 E. Slauson Ave, Huntington Park, CA 90255.

*(Continued on Page 458)*

(Continued from Page 457)

PHYSICIANS WANTED

## CALIFORNIA PRIVATE PRACTICE OPPORTUNITIES OB/GYN, FP, IM, PED

- Beneficial relationship with outstanding hospital
- Financial assistance to establish practice
- Smart office configuration with state-of-the-art equipment
- Expert office management, billing and collections

**Camden Management Services, Inc. — (818) 914-2286**

## PART-TIME MEDICAL CONSULTANT CONTRACTS

Physicians needed to work under contract, on a part-time basis for the Social Security Administration's Disability Insurance Program. Involves review of medical evidence in disability claims at 75 Hawthorne Street, San Francisco, California. No patient contact. Applicants must: (1) have a valid license to practice medicine in the USA; (2) have recent or current clinical experience; and (3) be available between 7:00 am and 5:30 pm, Monday through Friday for case review. Subject to change, the specialties needed are Cardiology, Pulmonary Medicine, Psychiatry, Neurology, Physical Medicine and Rehabilitation, Internal Medicine, Pediatrics, and Orthopedics. In addition to physicians for medical review, a chief medical consultant (Regional Medical Advisor) is needed. This is an administrative position and, in addition to the above criteria, three years experience in the Disability Program Branch is required. Applicants for this position should be available approximately 20 hours per week. Women and minorities are encouraged to apply. If interested in receiving further information, submit written request by April 30, 1990 to:

**Chief, Regional Acquisition and Management Branch**
**50 United Nations Plaza, Room 403**
**San Francisco, CA 94102**

**GENERAL INTERNIST, BC/BE,** needed for a position with suburban satellite clinic of a Seattle area, multispecialty group practice. Diverse patient population includes managed care, fee-for-service, retired and active military. Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

**EXCEPTIONAL GROUP PRACTICE OPPORTUNITY** for an Internist to join two other Internists. Located in southeastern Utah in the city of Price, near scenic national parks, great skiing, and other outdoor recreation. Excellent educational facilities including a junior college. Primary service area is approximately 30,000 people. Contact Tad Morley, Castleview Hospital, 300 N. Hospital Dr, Price, UT 84501; (801) 637-4800.

**INTERNISTS—SOUTHERN CALIFORNIA.** Forensic Medical Company looking for MD who is bright, creative, and able to assimilate facts into medical reports. Primarily Workers' Compensation referrals. Part-time initially. Send CV to D. Salrin, 3600 Wilshire Blvd, Ste 1908, Los Angeles, CA 90010; (213) 384-8200.

**ORTHOPEDIC SURGEON.** Orthopedic Surgeon for busy orthopedic service in 230-bed teaching hospital with residencies in General Surgery, Internal Medicine, OB/GYN, and Family Practice. Should be BC/BE. Experience in Arthroscopy preferred. Salary and compensation plan negotiable depending on experience. Hospital located in beautiful northern San Joaquin Valley close to major cities and skiing areas. Submit CV and references or contact Kenneth Young, MD, Chief of Orthopedics, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6611. AA/EOE.

KAISER PERMANENTE®

*Good People. Good Medicine*

## NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

**BC/BE INTERNIST** needed to practice Intensive Care Medicine for a busy, moderate-sized, multispecialty group practice, 25 miles south of San Francisco. Majority of practice based at a 400-bed state-of-the-art hospital, adjacent to the clinic. Excellent salary, vacation, and benefits. Ideal for recently BC/BE Internists awaiting fellowships in July 1991 for Pulmonary, Cardiology, or Critical Care Medicine. Send CV to Number 198, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIANS WANTED

## EUGENE CLINIC, EUGENE, OREGON

Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Family Practice, Geriatrics, Occupational Medicine, Orthopedics, Psychiatry, Urgency Care, Urology. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

**Physician Recruiter**
**1162 Willamette St**
**Eugene, OR 97401**

## UTILIZATION REVIEW POSITIONS

Cost Care, the nation's leading independent utilization management company, is seeking BC physicians to staff the medical services department. These part-time positions will include intensive training in all aspects of health care cost containment including pre-certification, home health care and case management. Prior Utilization Review experience is a plus, but not mandatory.

If you are seeking new skills in the changing health care marketplace, please submit your CV to:

**Alan R. Greenfield, MD, MBA**
**Vice President**
**Medical Services**
**COST CARE, Inc**
**17011 Beach Blvd, Ste 400**
**Huntington Beach, CA 92647**

**NORTHERN CALIFORNIA—SAN FRANCISCO BAY AREA.** Leading HMO is seeking BC/BE physician to staff a busy urban, full-service Emergency Department with the possibility of administrative advancement. Kaiser Permanente is a large pre-paid HMO offering competitive salary, job security, shareholder status, and generous benefits including health care, life insurance, disability insurance, sick leave, mortgage assistance, and educational leave. Please address all inquiries to David Witt, MD, Emergency Dept, Kaiser Permanente Medical Center, 1200 El Camino Real, South San Francisco, CA 94080-3299; or call (415) 742-2516. EOE.

**GENERAL INTERNIST.** Steinbeck country, BC/BE General Internist to join dynamic group; includes hospital care, shared call. Spanish helpful. Many visiting consultants, good guarantee with chance for early partnership. Many fringes. One hour to Monterey, three hours to San Francisco. Call or write Helen Poole, 210 Canal St, King City, CA 93930; (408) 385-5471.

**FAMILY PRACTITIONER.** Steinbeck country, BC/BE Family Practitioner to join dynamic group; includes hospital care, OB, shared call. Spanish helpful. Many visiting consultants, good guarantee with chance for early partnership. Many fringes. One hour to Monterey, three hours to San Francisco. Call or write Helen Poole, 210 Canal St, King City, CA 93930; (408) 385-5471.

(Continued on Page 459)

(Continued from Page 458)

PHYSICIANS WANTED

## OREGON/SOUTHWEST WASHINGTON

Excellent opportunities available for BC/BE Family Physicians in Oregon and southwest Washington. Openings available in the Portland/Vancouver area (full-time and half-time); Longview, Washington; and Salem, Oregon. Group provides a full range of professional services to 20,000 to 380,000 Kaiser Permanente members depending on location. Excellent salary/benefits; senior physician standing after two years; sabbatical; paid liability coverage.

Forward CV and inquiry to

**Regional Medical Director**
**Northwest Permanente**
**3600 N. Interstate Ave**
**Portland, OR 97227.**

**SACRAMENTO,** Internal Medicine or Family Practice. BC/BE with experience/training in Addiction Medicine. ASAM welcome. Kaiser Permanente has approximately 360,000 members in the Sacramento area. Active outpatient chemical dependency program. Hospital care for detox. No rehab. Dual diagnosis is handled by ourselves and psychiatry. At least 50 percent of time in addiction medicine with opportunity to evolve to full-time. Very attractive salary and full benefit package. Available in three months. Please contact David C. Meek, MD, Sub-chief, Alcohol and Drug Program, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825; or call (916) 978-1495. EOE.

**PEDIATRICIAN. MAKE AN IMPACT!** BC Pediatrician to join established practice across from a major medical center in Burbank. Employment leading to opportunity for partnership. You will have the freedom to practice the very best medicine. Send CV to Dr Anne Resnick, Ste 420, 2625 Alameda, Burbank, CA 91505.

**WHY NOT WALK TO WORK?** BC/BE General Internist in North Idaho. Enjoy unlimited rural possibilities and outdoor recreation. Practice with every amenity of an urban community with two major universities (25,000 students) in adjacent communities, PAC-10 and Big Sky. High quality of life with progressive 60-bed hospital possessing state-of-the-art capabilities including CT, MRI, nuclear medicine, and color doppler echo. Population of 40,000 in county. Our office is two years old, computerized, located in multiple practice facility adjacent to hospital. We offer a guaranteed salary with incentives, malpractice and health benefits with option for partnership after first year. Send CV to Fred Goodhue, Administrator, Centennial Internal Medicine, 623 S. Main, Moscow, ID 83843.

**BC/BE ORTHOPEDIC SURGEON** needed to join two physician department in a busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to a 400-bed, state-of-the-art hospital. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 198, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**INTERNIST BC/BE** needed to join thirteen physician department in busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Excellent salary, vacation, and benefits. Early partnership. Please send CV to Number 198, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIANS WANTED

## CALIFORNIA AND WESTERN STATES

Opportunities for BE/BC physicians in metropolitan and rural areas in Cardiology, Critical Care, Emergency Medicine, Endocrinology, ENT, Family, General Surgery, Internal Medicine, Neurology, Neurosurgery, OB/GYN, Orthopedics, Plastic Surgery, Pediatrics, Pulmonology, Rheumatology, and Urology. **Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.**

## GENERAL SURGEON

BC/BE needed to replace retiring partner in 16-physician multispecialty group. This unique opportunity is located in a friendly high desert community at the foot of the Sierras close to year 'round outdoor recreation. Excellent financial opportunity for a skilled surgeon with a generous compensation and executive benefit package. Our modern 25,000 square foot facility is immediately adjacent to a well equipped 80-bed hospital. Equal ownership is available after one year. Please send CV to:

**Gary Staab**
**1111 N. China Lake Blvd**
**Ridgecrest, CA 93555**
**(619) 446-4571**

**SACRAMENTO KAISER PERMANENTE.** BC/BE Family Practitioners needed to join large group of Family Practitioners providing ambulatory and inpatient care in a large prepaid health plan. Excellent working environment with strong specialty support. Outstanding financial package. Sacramento is a growing metropolitan area with good schools and recreational activities. Close to San Francisco and Lake Tahoe. If interested, please contact Stuart Hahn, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825; or call (916) 973-5546. EOE.

**PHOENIX AREA.** Behavorial Health Program seeking additional adult psychiatrist. Center provides child through adult inpatient, outpatient and partial hospitalization, adult and adolescent CD. Fee-for-service with shared call, or association with existing staff are options. Hospital provides competitive financial support. For more information, call Greg Peterson, E. G. Todd Associates, at (800) 776-7330, or collect (913) 341-7806.

## PROGRESSIVE MULTISPECIALTY GROUP

of over 20 physicians, located in Tracy, one of the most rapidly growing cities in northern California. Located in the San Joaquin Valley with diversified economy and excellent schools. We are looking for the following:

DERMATOLOGY
OTOLARYNGOLOGY
OB/GYN
NEUROLOGY
ORTHOPEDICS
PEDIATRICS
PODIATRY

Applicants must be BC/BE. Offering an excellent salary with an incentive arrangement and a competitive benefit package, leading to partnership after 18 months.

Reply with CV and references to:

**Physician Recruitment**
**Eaton Medical Group**
**445 W. Eaton Ave**
**Tracy, CA 95376**

## PHYSICIAN ADMINISTRATOR Southern California

CIGNA Healthplans of CA, a staff model HMO committed to providing innovative, quality health care to 400,000 members in southern CA, is seeking a primary care physician to assume the challenging responsibilities of Physician Administrator.

You will maintain an active clinical practice with a proportion of time dedicated to leadership and management of physician and support staff. Qualifications include Board Certification and prior management experience. Excellent compensation and benefit package, including bonus plan.

Call collect or send CV in confidence to:

**Professional Recruitment Dept.**
**CIGNA Healthplans of CA**
**505 N. Brand Blvd, Ste 400-49**
**Glendale, CA 91203**
**(818) 500-6236**

An Equal Opportunity Employer

**SAN FRANCISCO BAY AREA.** BE/BC Internist. We currently are seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 prepaid Health Plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to Winslow Wong, MD, Attn: Administration, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545. EOE.

**NORTHERN CALIFORNIA—SACRAMENTO.** Leading HMO is seeking a BC/BE inpatient and outpatient Family Practitioner. Inpatient responsibility extends to physicians' individual practice only. Emphasis on Internal Medicine, Gynecology, and Orthopedics. No OB, limited Pediatrics. Must work outpatient clinic one night per week and one weekend day per month. We offer many benefits including malpractice insurance, medical, dental, and group life insurance, vacation, sick, and educational leave, excellent retirement benefits, and special arrangements for physicians transferring from established practice. For more information, please send CV to Dr J. Berger, Kaiser Permanente Medical Center, 6600 Bruceville Rd, Sacramento, CA 95823. EOE.

## EMERGENCY MEDICINE CALIFORNIA'S NORTH COAST

BC/BE. Opportunity for a challenging Emergency Medicine practice at a Level II Emergency Services Facility with EMS base station designations, full range of trauma care and the majority of patient visits are urgent/emergency care. Practice development includes areas of occupational medicine. University community on the redwood coast with excellent schools, cultural and recreational activities. Call and/or send CV to:

**Physician Recruitment Committee**
**Mad River Community Hospital**
**PO Box 1115**
**Arcata, CA 95521**
**(707)822-3621, ext 263**

(Continued on Page 460)

(Continued from Page 459)

**BC/BE INTERNIST,** San Diego area to join community clinic. Flexible hours. Part-time or full-time. Hospital work if desired. Competitive salary and benefits. Send CV to Dr Eileen Hennrikus, National City Family Clinic, 1136 "D" Ave, National City, CA 92050; (619)474-0972.

**SAN FRANCISCO EAST BAY.** BC/BE Internist needed to join 10 physician primary care group practice in beautiful San Ramon Valley area. Excellent opportunity and compensation. Reply in confidence to Number 201, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**CALIFORNIA STATE UNIVERSITY, SACRAMENTO,** is seeking a qualified physician to assume the position of Medical Director for the University's Student Health Center. This position will be responsible to the Director of the Health Center for a staff of five physicians, developing and maintaining medical procedures, and providing direct primary medical care services. Qualifications include possession of an MD degree, valid license to practice medicine in California (or documentation of ability to obtain licensure by starting date), and current medical board certification in Family Practice, Obstetrics/Gynecology, Pediatrics-Adolescent Medicine, or Internal Medicine. Five years experience preferred, of which three years providing care to young adult population and two years in an administrative capacity. Application deadline is April 27, 1990. Send letter of application, résumé, and names and telephone numbers of three professional references to Office of Faculty and Staff Affairs, California State University, Sacramento, Box MD, 6000 J St, Sacramento, CA 95819. CSUS is an Affirmative Action/Equal Opportunity Employer.

**CALIFORNIA, MOTHER LODE COUNTRY.** Family Practice, General Practice in rural community health center. Excellent recreation area. Send CV or contact Randy Windsor, Executive Director, PO Box 897, Pioneer, CA 95666; (209) 295-5544.

**OREGON.** Family Practice opportunity in sunny southern Oregon. Three physicians seeking two associates, so bring a colleague! No Obstetrics. Great quality of life. Contact Mark Wood, Klamath Family Practice, (503) 883-8134.

## MENTAL HEALTH UTILIZATION REVIEW POSITIONS FOR PSYCHIATRISTS IN CALIFORNIA AND GEORGIA

Cost Care, Inc., the nation's leading independent utilization review company is seeking Psychiatrists to join the mental health services department on a part-time basis. The positions will include training in psychiatric/substance abuse utilization review and exposure in case management consultation.

The ideal candidates will possess:

- Five years clinical experience
- Board certification, preferred
- Strong interpersonal skills
- Prior managed care experience

Salary is commensurate with experience.

Send CV to:

**Dr Paul Gerhardt**
**Director Mental Health Services**
**Cost Care, Inc.**
**PO Box 2738**
**Huntington Beach, CA 92647**
**(714) 848-5764 ext 3700**

## GROWING, ESTABLISHED (1923)

35 physician multispecialty medical group with four locations in northeast central San Fernando Valley (north section of the Los Angeles City and County) seeks 1990/1991 BC/BE California licensed physicians in the following specialties:

INTERNAL MEDICINE
FAMILY PRACTICE
PEDIATRICS
OB/GYN
GENERAL SURGERY

Qualified candidates please send CV and references to:

**Mr Donald Abramsky, MBA**
**Administrator**
**Facey Medical Group, Inc.**
**11211 Sepulveda Blvd**
**Mission Hills, CA 91345-1196**
**(818) 365-9531**

**ASSISTANT PUBLIC HEALTH DIRECTOR.** Riverside County Health Department is recruiting for a newly created assistant department head position to direct day-to-day administration of all departmental programs. Candidates must be MDs and eligible for certification by American Specialty Board and have two years experience as a physician in a public health agency, at least one of which must be in an administrative capacity. For detailed requirements and application materials, contact Riverside County Personnel Dept, 4080 Lemon St, Room 109, Riverside, CA 92501-3664; (714) 275-3500. EO A A M/F/H.

**FAMILY PRACTICE PHYSICIAN.** Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

**SALT LAKE CITY, UTAH, FAMILY PRACTICE PHYSICIAN, BC/BE.** Excellent opportunity in Salt Lake suburb to join busy practice, near excellent skiing, hunting, and fishing. Our clinic operates six days a week, and our patients are from a growing Salt Lake suburban population. Excellent salary and benefits. A partnership opportunity will be available after two years. Send CV to Robert Davis, MD, Director, Family Medical Center, 1781 W. 90th S., West Jordan, UT 84092; (801) 562-9100.

**PRIMARY CARE, GENERAL INTERNIST OR FAMILY PRACTITIONER** BC/BE to join established Internist in satellite clinic 10 miles from main clinic across state line in Oregon. Main clinic is an expanding 31 physician multispecialty group. Guaranteed income plus excellent benefits. Send CV to Connie Goude, 55 W Tietan, Walla Walla, WA 99362.

**RADIOLOGIST—SAN FRANCISCO.** Opening for BC Diagnostic Radiologist at Mount Zion Hospital in San Francisco. MR, angiography, CT, ultrasound, general diagnosis. Please contact P. Brodey, MD, 1600 Divisadero St, San Francisco, CA 94115; (415) 885-7466.

**URGENT CARE/PRIMARY CARE PHYSICIANS** for over 90 positions available with various physician groups in Phoenix metropolitan/Tucson, Arizona. Excellent compensation and partnership opportunities. Contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

**RADIOLOGIST.** Immediate opening for BC General and Diagnostic Radiologist at teaching hospital near Seattle. Ultrasound, CT, and mammography, plus limited basic angiography and interventional skills. Washington license not required. Regular hours. Full-time or six to nine months per year. Five-year contract. Call Dr Bernstein, (206) 840-9652.

## HSI RESOURCES DIV.

Health Services Inc

### HEALTHCARE PERSONNEL SERVICES

HSI currently has numerous opportunities in California and Washington state for qualified physicians and Orthopedic Surgeons. These positions offer:

- Flexible hours and days.
- No on-call or mandatory weekends.
- Competitive salary plus bonus plan.
- Paid vacation, sick, holiday, and CME.
- 401 K retirement savings programs with matching contributions.
- Full medical/dental.
- Relocation assistance.
- Strict confidentiality.
- All fees paid by employer.

Call
**Jeannette Bezemer**
collect or write:
**HSI RESOURCES**
**2600 Michelson Dr, #1130**
**Irvine, CA 92715**
**(714) 476-9163**

**PEDIATRICIAN** BC/BE needed in northern suburb of San Francisco. Opportunity to join part of a multispecialty group. Applicant should demonstrate strong academic skills committed to quality personalized care. Forward CV to Peter Earley, Physician Relations, Ross Valley Medical Group, 2200 Larkspur Landing Circle, Ste 103, Larkspur, CA 94939.

**IMMEDIATE OPENING.** University affiliated ambulatory center. Full-time position available immediately in San Bernardino/Riverside, California. Competitive basic salary guarantee plus attractive fringe benefits. Contact Daniel Injo, MD, 22182 Barton Rd, Grand Terrace, CA 92324; (714) 370-1300.

**NATIONAL HAIR TRANSPLANT COMPANY** seeks physician with MD degree to perform hair restoration surgery in the west coast states. Excellent compensation and benefit package. Will train in new techniques. Good opportunity for a physician looking for a change in daily routine. Send CV to Richard P. Giannotti, MD, PC, Pembroke Four Building, Ste 210, Virginia Beach, VA 23462.

**EMERGENCY PHYSICIAN** to join established group at attractive, well-equipped emergency room, with excellent nursing, attending staff, in San Francisco. $100K per year. Malpractice paid. Contact Rob Hemmick, MD, 450 Stanyan St, San Francisco, CA 94117; (415) 750-5700.

## CALIFORNIA—MONTEREY

Well established four physician Internal Medicine group seeking replacement for one Internist leaving practice. Unique opportunity to practice primary care medicine in an office with full lab, x-ray, and shared call coverage. If you want to work hard in paradise—call us. 1 (408) 373-3153.

(Continued on Page 461)

(Continued from Page 460)

## PHYSICIANS WANTED

**LIVE AMONG THE REDWOODS.** Successful surgeon seeks partner for busy General and Vascular Surgery practice on northern California coastline. 85-bed hospital supportive of practice—will provide guarantee and malpractice. Call Gwyneth Anderson for more details about this ideal opportunity at (800) 221-4762, or collect (212) 599-6200. E. G. Todd Associates, 535 Fifth Ave, Ste 1100, New York, NY 10017.

## PRACTICES AVAILABLE

**OB/GYN,** Beach City. Doctor leaving state. $400K gross 1989. Asking $100K. Financing available for qualified buyer. N. Newton, (818) 445-0458.

**GENERAL PRACTICE CLINIC FOR SALE.** Established 25 years. Supports two physicians, physician assistant. X-ray and pharmacy on premises. Spanish helpful. Large hospitals nearby. California central valley near educational and recreational facilities. Ideal for family living. Reply to Number 189, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**INTERNAL MEDICINE**—San Diego City, high development area. Gross $160,000. Low overhead with high net cash flow. Contact Practice Consultants, (619) 528-2321, Dr Bernard Press, Broker.

**INTERNAL MEDICINE OR FAMILY PRACTICE.** Beautiful Point Loma, San Diego, California. Well established solo Family Practitioner. Will introduce. Reliable call group. Great 250-bed hospital support. (619) 223-1666.

**INTERNIST/FAMILY PRACTICE,** Whitefish, Montana. $230,000 per year adult practice/weight clinic. Seven miles from ski resort, 20 miles from Glacier Park. $65,000 price includes $50,000 assets. Transition assistance. Women encouraged to apply. (406) 862-2270.

**SOUTHERN CALIFORNIA** General Practice for sale. High volume practice in fast growing area. Internal Medicine or General/Family Practice. Palm Springs weather, two hours from San Diego. Price and terms negotiable. Reply to Number 192, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**NORTHERN AND CENTRAL CALIFORNIA.** Established practice available. Dermatology, Family, Internal Medicine, OB/GYN, Ophthalmology, Pediatrics, Plastic Surgery, and Urology. Reasonable terms and prices. Call/write Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.

**REGIONAL ORTHOPEDIC PRACTICES.** Lucrative orthopedic practices available with several midwestern regional medical centers. Unique opportunities with highly competitive start up compensation packages which include income guarantees, paid malpractice, and moving allowance along with additional desirable benefits. These are modern facilities with excellent peer association and up to date surgical equipment. Several locations available! Call Gwyneth Anderson at (800) 221-4762, or write to E. G. Todd Associates, 535 Fifth Ave, Ste 1100, New York, NY 10017.

**LOS GATOS—FAMILY PRACTICE** (San Jose Area). Available July 1, 1990. Retiring MD (four Family Practitioners in group). Call Dr G. Bruce, (408) 377-9186.

**INTERNAL MEDICINE** practice available, Prescott, Arizona. A fine group of regular patients. Excellent living, facilities, coverage. Call for details (602) 445-2335 after 6 pm. Expanding territory.

**29 YEARS GENERAL MEDICAL PRACTICE** and well equipped office for sale in a suburban, well situated university town of northern California wine country. Retiring July 1990. Reply to Number 194, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

## PRACTICES AVAILABLE

**WELL ESTABLISHED GENERAL INTERNIST'S PRACTICE.** Excellent coverage and income. Silicon Valley. Physician will retire incrementally. U.S. trained BE/BC only, please. Reply to Number 178, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**BEAUTIFUL NAPA VALLEY, CALIFORNIA.** Solo Psychiatric practice. Good clientele. Potential for growth as desired. Physician retiring. Residence available. Call David Lucchesi, (707) 552-3831.

**FAMILY PRACTICE**—San Diego North County Inland. Gross $256,000. Mature quality practice with excellent patient base. Well located 2,000 square foot office. No Medi-Cal. Practice Consultants (619) 528-2321.

**CORONA, SOUTHERN CALIFORNIA.** Great opportunity to take over a busy established Internal Medicine/Pulmonary Disease practice. Good coverage. Excellent income. Negotiable terms. Reply to Number 199, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**PLASTIC SURGERY PRACTICE** available. Long established practice in growing area of central California. Retiring physician willing to stay to introduce. Contact Bradshaw Associates, (415) 376-0762.

**SAN DIEGO.** Panoramic ocean view. Family Practice/Internal Medicine. Fully equipped clinic, long established practice of 25 years, doctor retiring, hospital financial assistance to start. 2,000 square feet. Reasonable. (619) 456-9330.

**FAMILY PRACTICE AVAILABLE.** Large practice next to community hospital in Ogden, Utah. Established five years, new equipment, full computer system. Reply to Number 196, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**SUBURBAN GERIATRIC PRACTICE.** 27 K-1989. Reply to Number 195, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**SAN DIEGO COUNTY.** Cardiology, Internal, OB/GYN and Pediatric Practices available. Long established—doctors retiring. Various prices and low down payments. Call CBI, San Diego County's professional practice sales specialists, (619) 283-7009.

## POSITION WANTED

**CARDIOLOGIST INVASIVE/CERTIFIED INTERVENTIONAL**

Extensive PTCA experience, seeking association with prestigious group. Reply to Number 187, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

## PLACEMENT SERVICES

**AT LAST!** Western Practitioner Resources places nurse practitioners, physician assistants, and certified nurse midwives in your clinical setting. Please phone Heidi Bourne, Director, (800) 345-5859 or (707) 839-5859.

## LOCUM TENENS

**ENT LOCUM TENENS** available anytime. 23 years practice experience. BC. Licensed in California, Nevada, and Wyoming. CV and references upon request. Call (702) 831-7636. K. M. Holmes, MD. Leave message.

**GENERAL PRACTITIONER,** 41 years old, seeks locum tenens in New Mexico. Two to four week periods. Quality medical care, negotiable prices. No placement company involved. Reply to Number 200, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

## LOCUM TENENS

**locum tenens: "the interim solution"**

Why make a long-term commitment *before* you really want to? Until you're ready to "sign on the bottom line"... enjoy freedom, flexibility, and professional satisfaction as a PRN *locum tenens* physician. Call us toll-free for details.

The **PRN** Physicians
1-800-531-1122
Member Interim Physician Placement℠

Your Access to Quality Physicians and Practice Opportunities.
**1-800-462-6573**
LOCUM TENENS, INC.
A Division of Jackson and Coker
With offices in Atlanta and Denver
115 Perimeter Center Place
Suite 380-WJML0
Atlanta, GA 30346

*Ads Get Results!*

**WESTERN PHYSICIANS REGISTRY**
**Locum Tenens Service**
**Permanent Placement**

Since 1980, WPR has served the needs of California's physicians. When someone needs coverage or ongoing, part-time help, we find the right physician. When a practice must expand, we find a permanent associate. We pride ourselves on our discretion, our very personal service matching the right person with the right job. We work only in California, concentrating our efforts where we know our market. Our clients include private practices, HMOs, urgent care centers, emergency departments, multispecialty groups, and community clinics.

**Northern California, Carol Sweig and Jim Ellis, Directors, (415) 673-7676 or (800) 437-7676**

**Southern California, Tracy Zweig, Director, (818) 999-1050 or (800) 635-3175**

(Continued on Page 462)

(Continued from Page 461)

**ALBUQUERQUE, NEW MEXICO** prime medical office for rent. Five minutes from two major hospitals. 1,250 square feet, four examining rooms, business office with restroom and shower, patient's restroom, x-ray room, lab area, reception room, good views. All utilities, maintenance paid, owner's home (505) 662-6222.

**GROWTH AREA OF SANTA CLARA VALLEY.** New medical office space for lease in the growth area of Silicon Valley, Morgan Hill, California. Easy access, abundant parking, well located, generous tenant improvement allowances. Excellent patient referral sources. Contact Dr Jon Hatakeyama, (408) 779-7391.

## DON'T FORGET!

The deadline for submitting classifieds for the June issue of WJM is April 25. Send your advertisement to

**Classified Advertising**
**WJM, PO Box 7602**
**San Francisco, CA 94120-7602**

## CT SCANNER FOR SALE

Compact, two console Philips Tomoscan 60 with Multiformat Camera; Fully serviced and upgraded by Philips: Excellent performance; Quality images; Ideal for private practice, hospitals, clinics, or as second unit.

**FINANCING AVAILABLE**

Contact:
**Claudia Gray or**
**Jim Maffetore**

**NATIONAL MEDICAL REMARKETING**
**Bell Atlantic-Tricon**
**Medical Finance Division**

**(714) 641-1984**
**(800) 633-1984 Outside California**

**OHIO UNITROL ANESTHESIA MACHINE** with Ohio V5A ventilator and two precision vaporizors (ethrane and forane): $4,000. Bruggerman "crank-up" over table: $200. Two stainless steel utility tables with drawer: $100 each. Ohio 2000 and Ohio 4000 anesthesia with ventimeter ventilator machines: $750 each. Contact Janet, (415) 937-7100.

**BURDICK 310** 3-channel EKG. Survalent electronic thermometer; Pocket Doppler (OB). All nearly new. Make offer. (208) 587-8038.

**OPHTHALMIC** equipment and supplies for sale (like new). Readily available in Merced, central California. Doctor trying to retire—equipment two to three years old. Full line of Humphreys equipment including office computer with electronic billing, auto refractor, A scan, auto 'K,' lens analyser, field analyser, AT&T four lane Merelene telephone system, Argon and Yag lasers, office furniture, full ophthalmic library. All you need to start fresh office is available. (209) 383-2657.

**$5,000-$60,000 FOR PHYSICIANS.** Unsecured signature loans for any need including taxes, debts, investments, etc. No points or fees. Best rates. Level payments up to six years—no prepayment penalty. Call toll free 1 (800) 331-4952, MediVersal Department 114.

**2V MEDTECH INTERNATIONAL CORP.**

DIAGNOSIS — 2V STAT™ — TREATMENT

PRESENTS

**2V STAT** Medical Decision Support Software Covering 69 Specialties—Algorithms and Text

PLUS

**COMPUTER** 80286/12 MHz Turbo CPU 80 MB HD, EGA Color Monitor, Color Graphic Card 40 MB Back-up Drive, and Printer

**$5962**
(for complete system)

**ORDER NOW!**
**1•800•228•STAT**
Technical Support Call 1•404•956•1855

2450 Winds Hill Road, Suite 201 • Marietta, Georgia 30067
Fax 404•956•7068 Telex 551341 MedVideo FasyLink 622779660

## CME IN OREGON

***Summer Ashland Conference:***
**Gastroenterology**
**June 22-23, 1990**
Ashland Hills Inn, Ashland, OR

***Summer CME at Sunriver:***
**Pulmonary & Critical Care Med.**
**Suturing Techniques**
**July 23-27, 1990**
Sunriver Lodge & Resort
Sunriver, OR

***Fall Ashland Conference:***
**Neurology in Primary Care**
**September 7-8, 1990**
Ashland Hills Inn, Ashland, OR

***Salishan Conference:***
**Cardiology**
**October 12-14, 1990**
Salishan Lodge,
Gleneden Beach, OR

For further information contact:
**Continuing Medical Education**
**Oregon Health Sciences Univ**
**Portland, OR 97201-3098**
**(503) 279-8700**

**CURRENT CONCEPTS IN CARDIOLOGY**

July 29-August 2, 1990. Lake Tahoe, Nevada. Fees: $455 for ACC members; $505 for nonmembers; $335 for residents, fellows-in-training, nurses, and technicians. 17.5 Category 1 credit hours. For information call **American College of Cardiology, (800) 253-4636; in Maryland (301) 897-5400.**

## WORKSHOP ON FALLOPIAN TUBE CATHETERIZATION

**Oregon Health Sciences University**
**Portland, Oregon**
**June 16-17, 1990**

- Offers hands-on didactic instruction in new transcervical methods for fallopian tube catheterization.
- Designed for gynecologists and radiologists with a sub-specialty interest in infertility
- Lectures address a variety of clinical applications and are supplemented by small group discussions.
- Includes practical experience using catheter devices in life-size models and opportunity to view video tapes in a workshop setting
- Tuition Fee: $400 (hospital group rate available
- **Course Directors:** Miles J. Novy, MD and Amy Thurmond, MD
- **Guest Speaker:** Richard Marrs, MD

For further information contact:
**Continuing Medical Education**
**Oregon Health Sciences Univ**
**Portland, OR 97201-3098**
**(503) 279-8700**

*Ads Get Results!*

**CLASSIFIED ADVERTISING INFORMATION**

**(415) 541-0900, Ext 376**

The Western Journal of Medicine

SINCE 1902 • CIRCULATION 56,000+

# Classified Advertisements

The rate for each insertion is **$7 per line** (average six words per line) **with five line ($35) minimum.** A confidential box number (in lieu of your address) can be assigned to your advertisement for $5 each month. The replies to the box number will be directly forwarded to you as they arrive at *WJM*'s office.

**Classified display rates $50 per inch. Maximum sizes: 1 column by 10 inches or 2 columns by 5 inches. Larger classified ad space by special arrangements.**

Copy for classified advertisements should be received not later than **25th of the second month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

**Please Type or Print Advertising Copy**

## Classified Advertisements Are Payable in Advance

THE WESTERN JOURNAL OF MEDICINE
P.O. BOX 7602, SAN FRANCISCO, CA 94120-7602
(415) 541-0900 EXT. 376

## ad copy

Print or Type Clearly

Number of lines _____ × $7 = $_____

Optional: Confidential box number charge: +$5 = _____

**Subtotal (minimum $35 *or* minimum $40 with confidential box number)** $_____

Number of insertions _____ × $_____ = (subtotal)

**Check enclosed for:** $_____

Name (Please Print)

Contact

Address

City/State/Zip

(_____)_____
Phone

Signature

## WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

**Alaska State Medical Association**—2401 E 42nd Ave, Suite 104, Anchorage 99508. (907) 562-2662. Annual Meeting: June 7-9, 1990, Alaska Land, Fairbanks.

**Arizona Medical Association, Inc**—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 7-9, 1990, Wyndham, Paradise Valley.

**California Medical Association**—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-8, 1991, Bally's Grand Hotel, Reno.

**Colorado Medical Society**—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 13-16, 1990, Keystone.

**Hawaii Medical Association**—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 12-14, 1990, Ilikai, Honolulu.

**Idaho Medical Association**—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 26-28, 1990, Sun Valley.

**Montana Medical Association**—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 4-6, 1990, Sheraton, Billings.

**Nevada State Medical Association**—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: June 21-23, 1990, Hyatt, Lake Tahoe.

**New Mexico Medical Society**—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 4-5, 1990, Albuquerque.

**Oregon Medical Association**—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1991, date and location to be announced.

**Utah Medical Association**—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 12-14, 1990, Marriott Hotel, Salt Lake City.

**Washington State Medical Association**—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 19-22, Sheraton, Spokane.

**Wyoming Medical Society**—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 14-16, 1990, Jackson Lake Lodge, Moran.

## ADVERTISING INDEX


AMERICAN ACADEMY OF PAIN MANAGEMENT ..... 364

BURROUGHS WELLCOME
*Zovirax* ..... 367, 368

CLASSIFIED ADVERTISING ..... 453, 454, 455, 456, 457, 458, 459, 460, 461, 462

CNA INSURANCE COMPANY ..... 343

ELI LILLY & COMPANY
*Humulin* ..... 355

FHP HEALTH CARE ..... 457

HOFFMANN-LA ROCHE LABORATORIES
*Librax* ..... 344, 345
*Medication Education* ..... 369, 370
*Valium* ..... 3rd and 4th covers

KAISER PERMANENTE ..... 455

THE MGIS COMPANIES ..... 347

MEAD JOHNSON PHARMACEUTICAL DIVISION
*BuSpar* ..... 353, 354

MERCK SHARP & DOHME
*Vasotec* ..... 2nd cover, 341, 342

PALISADES PHARMACEUTICALS INC.
*Yocon* ..... 350

PHYSICIAN INTERINDEMNITY ..... 361

POSTGRADUATE MEDICINE ..... 371

PRIME CLINICAL SYSTEMS INC. ..... 373

G.D. SEARLE & COMPANY
*Calan SR* ..... 357, 358

SENIOR PATIENT ..... 365

SIMMONDS ..... 363

SK&F LAB COMPANY
*Dyazide* ..... 376

UNIVERSITY MICROFILM ..... 360

THE UPJOHN COMPANY
*Rogaine* ..... 348, 349, 350

US AIR FORCE ..... 375

THE WESTERN JOURNAL OF MEDICINE
*Special Issues* ..... 351
*Subscription* ..... 354

SARY MAY NOT SUBSTITUTE BRAND NECESSARY N.D.P.S. MAY NOT
NOT SUBSTITUTE DISPENSE AS WRITTEN NO SUBSTITUTION BRAND
Y MEDICALLY NECESSARY N.D.P.S. MAY NOT SUBSTITUTE MEDICA
TITUTE DISPENSE AS WRITTEN DO NOT SUBSTITUTE BRAND NECESSA
SUBSTITUTE N.D.P.S. NO SUBSTITUTION MEDICALLY NECESSARY N
ECESSARY BRAND NECESSARY MAY NOT SUBSTITUTE N.D.P.S. MA
. DO NOT SUBSTITUTE DISPENSE AS WRITTEN NO SUBSTITUTION B
SSARY MEDICALLY NECESSA ITUTE ME
E DISPENSE AS WRITTEN D CESSARY
TITUTE N.D.P.S. NO SUBSTIT Y NO SUB
SARY MAY NOT SUBSTITUTE MAY NOT
D NOT SUBSTITUTE DISPENSE
Y MEDICALLY NECESSARY
TITUTE DISPENSE AS WRITTE
SUBSTITUTE N.D.P.S. NO SU

TELEPHONE: 000-0000 REG. NO. 0000000
LIC: 000000

TTEBANN M. NRNGEE, M.D.
10 Main Street
Anytown, U.S.A. 00000

Name _____ Age _____
Address _____ Date _____

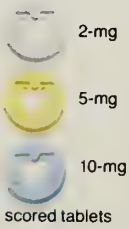
℞

Valium
5mg #30

Do not substitute

WHICHEVER WAY YOU WRITE IT...
WRITE IT FOR

VALIUM®
brand of
diazepam/Roche® IV




IT MAKES THE PRESCRIBING DECISION YOURS.

ROCHE®

SOMETHING TO THINK ABOUT...

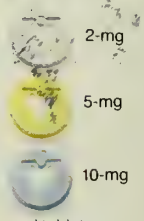
# THE PRACTICE, THE PATIENTS, THE PRESCRIPTIONS ARE YOURS.

KEEP THE PRESCRIBING DECISION YOURS, TOO

SPECIFY: DISPENSE AS WRITTEN

VALIUM®
brand of
diazepam/Roche ⓥ

The cut out "V" design is a registered trademark of Roche Products Inc.



scored tablets

YOUR CHOICE ALL ALONG!

ROCHE®
Roche Products

Roche Products Inc.
Manati, Puerto Rico 00701

Copyright © 1989 by Roche Products Inc. All rights reserved

COUNTWAY LIBRARY
OF MEDICINE
EXCHANGE OFFICE
10 SHATTUCK STREET
BOSTON, MA 02115-6011

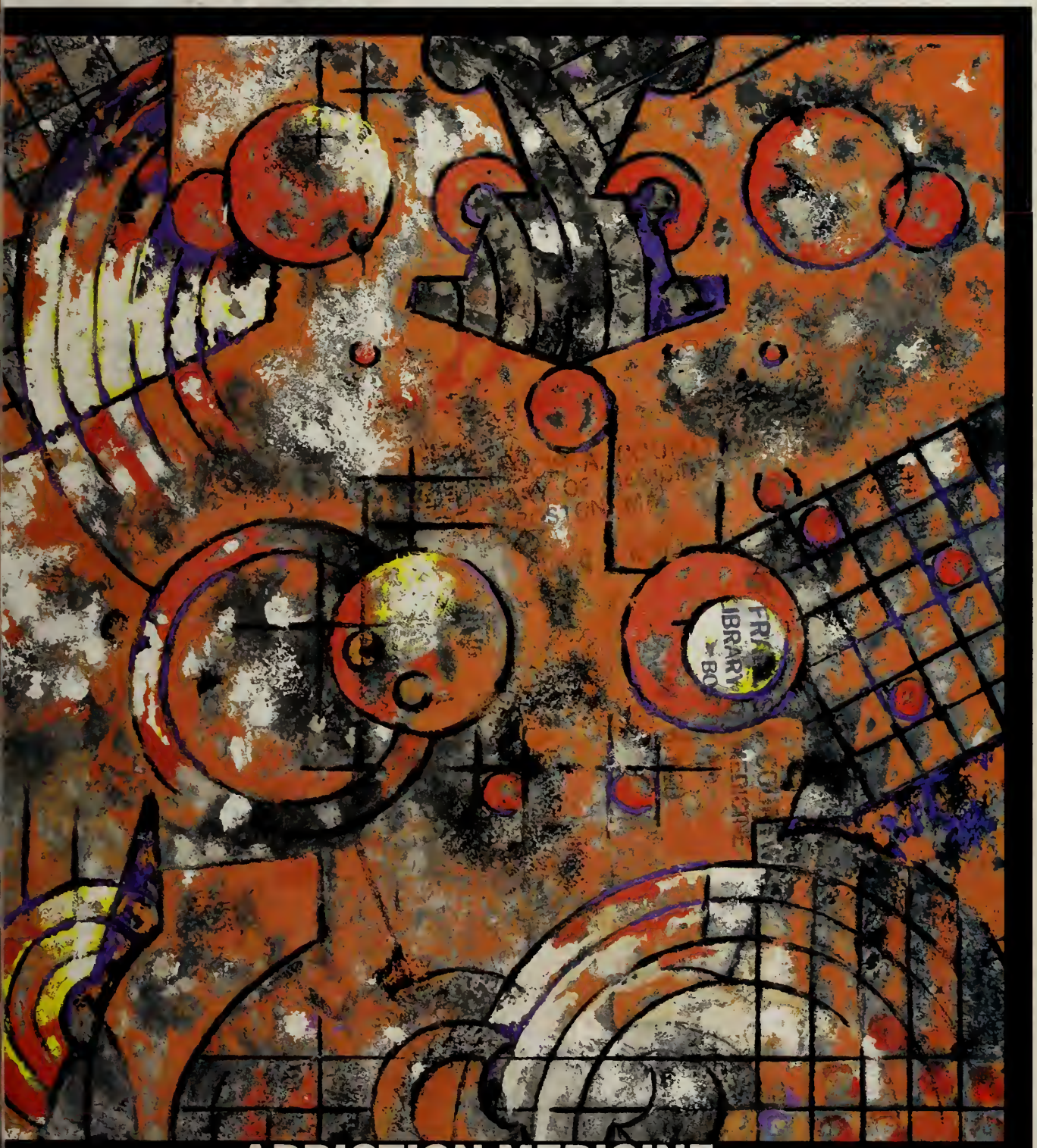
Arizona Medical Association
ARIZONA MEDICINE—PAGE 498

DISPLAY
SHELVES

# ie western ournal of Medicine

152 • NUMBER 5

MAY 1990



## ADDICTION MEDICINE

# THERAPY THAT MAY BE AS SILENT AS HYPERTENSION ITSELF

VASOTEC® (Enalapril Maleate, MSD) is generally well tolerated and not characterized by certain undesirable effects associated with selected agents in other antihypertensive classes.

VASOTEC is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

A diminished antihypertensive effect toward the end of the dosing interval can occur in some patients.

For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

Copyright © 1989 by Merck & Co., Inc.

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON, MA
JUN - 6 1991

FOR MANY HYPERTENSIVE PATIENTS
ONCE-A-DAY
VASOTEC®
(ENALAPRIL MALEATE | MSD)

# VASOTEC®

## (ENALAPRIL MALEATE | MSD)

VASOTEC is available in 2.5-mg, 5-mg, 10-mg, and 20-mg tablet strengths.

**Contraindications:** VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor

**Warnings:** *Angioedema* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms Angioedema associated with laryngeal edema may be fatal **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

*Hypotension:* Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone Patients with heart failure given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed, caution should be observed when initiating therapy (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary

*Neutropenia/Agranulocytosis:* Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered

**Precautions:** *General Impaired Renal Function* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy In such patients, renal function should be monitored during the first few weeks of therapy

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic This is more likely to occur in patients with preexisting renal impairment Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required

**Evaluation of patients with hypertension or heart failure should always include assessment of renal function.** (See DOSAGE AND ADMINISTRATION )

*Hyperkalemia* Elevated serum potassium (>5 7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials In most cases these were isolated values which resolved despite continued therapy Hyperkalemia was a cause of discontinuation of therapy in 0 28% of hypertensive patients In clinical trials in heart failure, hyperkalemia was observed in 3 8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions* )

*Surgery/Anesthesia* In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion

*Information for Patients*

*Angioedema* Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician

*Hypotension:* Patients should be cautioned to report lightheadedness, especially during the first few days of therapy If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

*Hyperkalemia* Patients should be told not to use salt substitutes containing potassium without consulting their physician.

*Neutropenia* Patients should be told to report promptly any indication of infection (e g , sore throat, fever) which may be a sign of neutropenia

NOTE As with many other drugs, certain advice to patients being treated with enalapril is warranted This information is intended to aid in the safe and effective use of this medication It is not a disclosure of all possible adverse or intended effects

*Drug Interactions*

*Hypotension, Patients on Diuretic Therapy* Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION )

*Agents Causing Renin Release:* The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e g , diuretics).

*Other Cardiovascular Agents* VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions

*Agents Increasing Serum Potassium:* VASOTEC attenuates potassium loss caused by thiazide-type diuretics Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC

*Lithium:* Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

*Pregnancy – Category C:* There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies of enalapril in pregnant women. However, data are available that show enalapril crosses the human placenta Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined, VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity.

*Nursing Mothers* Milk in lactating rats contains radioactivity following administration of $^{14}C$ enalapril maleate It is not known whether this drug is secreted in human milk Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

*Pediatric Use* Safety and effectiveness in children have not been established

**Adverse Reactions:** VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients

*HYPERTENSION* The most frequent clinical adverse experiences in controlled trials were headache (5 2%), dizziness (4 3%), and fatigue (3%)

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1 4%), rash (1 4%), cough (1.3%), orthostatic effects (1 2%), and asthenia (1.1%).

*HEART FAILURE* The most frequent clinical adverse experiences in both controlled and uncontrolled trials were dizziness (7 9%), hypotension (6 7%), orthostatic effects (2 2%), syncope (2 2%), cough (2 2%), chest pain (2 1%), and diarrhea (2.1%)

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were fatigue (1 8%), headache (1 8%), abdominal pain (1.6%), asthenia (1 6%), orthostatic hypotension (1.6%), vertigo (1 6%), angina pectoris (1.5%), nausea (1 3%), vomiting (1 3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%)

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0 5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category

*Cardiovascular* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*), pulmonary embolism and infarction, pulmonary edema, rhythm disturbances, atrial fibrillation, palpitation.

*Digestive:* Ileus, pancreatitis, hepatitis (hepatocellular or cholestatic jaundice), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth

*Musculoskeletal* Muscle cramps

*Nervous/Psychiatric* Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia

*Urogenital* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

*Respiratory* Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection.

*Skin* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, hyperhidrosis

*Special Senses* Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgias/arthritis, myalgias, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash, and other dermatologic manifestations

*Angioedema* Angioedema has been reported in patients receiving VASOTEC (0 2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS )

*Hypotension.* In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0 5% of patients following the initial dose or during extended therapy Hypotension or syncope was a cause for discontinuation of therapy in 0 1% of hypertensive patients In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2 2% of patients Hypotension or syncope was a cause for discontinuation of therapy in 1 9% of patients with heart failure. (See WARNINGS )

*Clinical Laboratory Test Findings*

*Serum Electrolytes* Hyperkalemia (see PRECAUTIONS), hyponatremia

*Creatinine, Blood Urea Nitrogen* In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0 2% of patients with essential hypertension treated with VASOTEC alone Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1 2% of patients.

*Hemoglobin and Hematocrit* Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0 3 g% and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0 1% of patients discontinued therapy due to anemia

*Other (Causal Relationship Unknown):* In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported A few cases of hemolysis have been reported in patients with G6PD deficiency

*Liver Function Tests.* Elevations of liver enzymes and/or serum bilirubin have occurred.

**Dosage and Administration:** *Hypertension* In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS ) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions* )

The recommended initial dose in patients not on diuretics is 5 mg once a day Dosage should be adjusted according to blood pressure response The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

*Dosage Adjustment in Hypertensive Patients with Renal Impairment* The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2 5 mg once daily The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily

*Heart Failure:* VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2 5 mg once or twice daily After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects.*) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

*Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia* In patients with heart failure who have hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine >1 6 mg/dL, therapy should be initiated at 2 5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, *Heart Failure,* WARNINGS, and PRECAUTIONS, *Drug Interactions.*) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg

*For more detailed information, consult your MSD Representative or see Prescribing Information, Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486* J9VS54R3(819)

MSD
MERCK SHARP & DOHME

# TAKE A CLOSER LOOK

*at MGMA's Professional Liability Program...it may just expand your group's coverage and lower your cost.*

- Combined purchasing power of participating MGMA member groups.
- A.M. Best A+ (Superior) rated carriers.
- Exclusive to qualified MGMA member groups.
- Prior Acts coverage.
- Flexible limits of liability.
- Retrospective dividends.
- No cost reporting endorsement for disability or death.
- No cost reporting endorsement after 5 years and age 55.
- Other exclusive reporting endorsement benefits.

For more than 20 years, thousands of MGMA member groups have been provided with sound employee benefit insurance plans through The MGIS Companies. Now may be a good time for you to find out more about medical-professional liability plans offered exclusively to MGMA member groups.

Dividends are not guaranteed. Not all features available in all States.

the mgis companies

*National Program Manager:*

**MGIS Property & Casualty Insurance Services, Inc.**

85 Great Oaks Boulevard, San Jose, CA 95119
Post Office Box 23400, San Jose, CA 95153-5351
408-365-3799 Toll Free: 800-969-MGIS Fax: 408-226-0271

*The Western Journal of Medicine*

(ISSN 0093-0415/USPS 084 480) is published monthly for $30 per year (USA and Canada) by the California Medical Association, 221 Main Street, San Francisco, CA 94105. Second-class postage paid at San Francisco, CA and additional mailing offices.

**POSTMASTER:**
Send address changes to
*The Western Journal of Medicine*
Circulation, P.O. Box 7602
San Francisco, CA 94120-7602

# *Moving?*

Please give us six weeks notice and supply your personal reference number.

**ID No.**

**302703 XX**

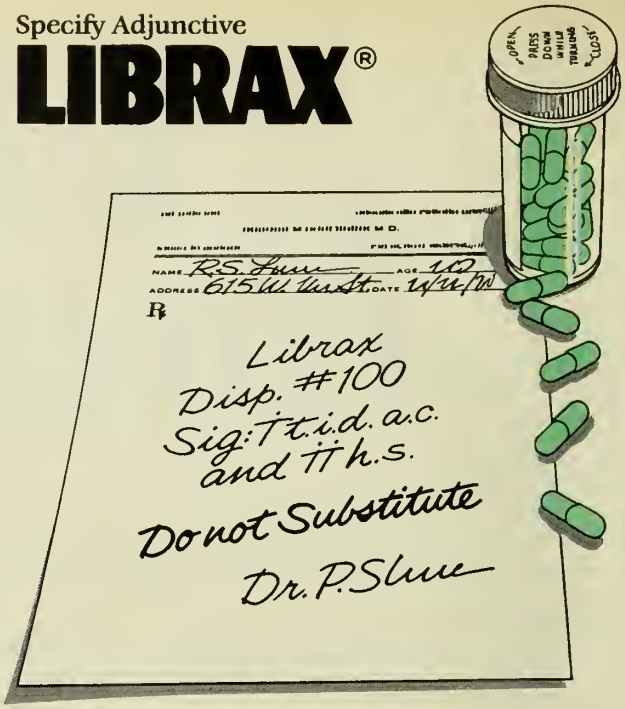
**The Western Journal of Medicine**
**P.O. Box 7602**
**San Francisco, CA 94120-7602**

**The Western Journal of Medicine**

**P.O. Box 7602**
**San Francisco, CA 94120-7602**

Specify Adjunctive

**LIBRAX®**




Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

* Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

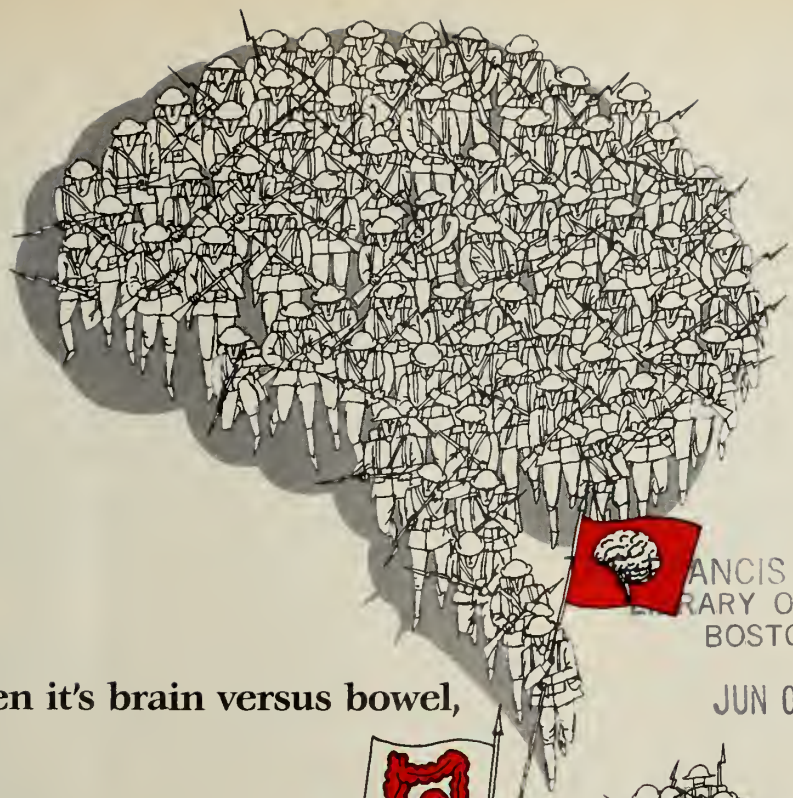
Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
*Usage in Pregnancy*: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

P.I. 0288

ROCHE® **Roche Products**

Roche Products Inc.
Manati, Puerto Rico 00701

Be sure to specify Librax, "Do not Substitute" or your state's equivalent statement on your prescription.



ANCIS A. COUNTWAY
RARY OF MEDICINE
BOSTON, MA

JUN 0 6 1990

**In IBS,* when it's brain versus bowel,**

# IT'S TIME FOR THE PEACEMAKER.

**In irritable bowel syndrome,*** intestinal discomfort will often erupt in tandem with anxiety—launching a cycle of brain/bowel conflict. Make peace with Librax. Because of possible CNS effects, caution patients about activities requiring complete mental alertness.

*Librax has been evaluated as possibly effective as adjunctive therapy in the treatment of peptic ulcer and IBS.

Specify Adjunctive

# LIBRAX®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

ROCHE

Copyright © 1989 by Roche Products Inc. All rights reserved.

Please see summary of prescribing information on adjacent page.

# The Western Journal of Medicine

SINCE 1902 ISSN 0093-0415

PO BOX 7602 • SAN FRANCISCO, CALIFORNIA 94120-7602 • TELEPHONE (415) 541-0900



LINDA HAWES CLEVER, MD, *Editor*
LLOYD H. SMITH, Jr, MD, *Associate Editor*
DIANA L. McANINCH, *Managing Editor*
SALLY LINEBARGER, *Assistant Managing Editor*
SANDRA WILLETT, *Editorial Assistant*
JANICE ANDERSEN, *Senior Copy Editor*
FRITZ C. HEATON, *Advertising and Promotion Manager*
NILA J. NICHOLS, *Circulation Coordinator*
DOROTHY A. HEARST, *Classified Advertising*

editorial communications to DR CLEVER • business communications to MS McANINCH



Official Journal of the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.



## EDITORIAL BOARD

*Editor Emeritus*
Malcolm S. M. Watts, San Francisco, Calif

*Editor Emeritus*
Dwight L. Wilbur, San Francisco, Calif

*Editor for Clinical Investigation*
Kenneth D. Gardner, Jr, Albuquerque, NM

*Special Editor for Arizona*
Marshall B. Block, Phoenix, Ariz

*Special Editor for Denver*
David Shander, Denver, Colo

*Special Editor for Idaho*
E. R. W. Fox, Coeur d'Alene, Idaho

*Special Editor for Nevada*
Anton P. Sohn, Reno, Nev

*Special Editor for New Mexico*
I. Brian Taylor, Carlsbad, NM

*Special Editor for Utah*
John H Holbrook, Salt Lake City, Utah

*Special Editor for Washington*
David Hopkins, Federal Way, Wash

*Special Editor for Wyoming*
Joseph P. Murphy, Casper, Wyo

*Allergy*
Merle S. Scherr, Scottsdale, Ariz

*Anesthesiology*
Ronald D. Miller, San Francisco, Calif

*Biostatistics and Epidemiology*
Virginia L. Ernster, San Francisco, Calif

*Cardiac and Thoracic Surgery*
Norman E. Shumway, Stanford, Calif

*Chest Diseases*
Leonard D. Hudson, Seattle, Wash
Thomas L. Petty, Denver, Colo

*Dermatology*
Clark Huff, Denver, Colo
Frank Parker, Portland, Ore
Gerald D. Weinstein, Irvine, Calif

*Emergency Medicine*
William A. Boehm, Alamogordo, NM
W. Richard Bukata, Flintridge, Calif
Clark Chipman, Portland, Dre
Thomas Elmendorf, Davis, Calif

*General and Family Practice*
Charles W Huff, Casper, Wyo
Norman Kahn, Sacramento, Calif
J. Jerome Wildgen, Kalispell, Mont

*Internal Medicine*
Philip R. Alper, Burlingame, Calif
Robert W. Burroughs, Spokane, Wash
Patricia Gabow, Denver, Colo
Harry R. Kimball, Boston, Mass
Darwin Palmer, Albuquerque, NM
George A. Porter, Portland, Dre
Irwin J. Schatz, Honolulu, Hawaii
Stephen I. Wasserman, San Diego, Calif
Laurens P. White, San Francisco, Calif

*Neurology*
J. Richard Baringer, Salt Lake City, Utah
Don F. Seelinger, Albuquerque, NM
W C. Wiederholt, La Jolla, Calif

*Neurosurgery*
George A. Djemann, Seattle, Wash
Robert F. Spetzler, Phoenix, Ariz
Charles B. Wilson, San Francisco, Calif

*Nuclear Medicine*
Philip Matin, Roseville, Calif

*Obstetrics and Gynecology*
Daniel Mishell, Jr, Los Angeles, Calif
Morton A. Stenchever, Seattle, Wash

*Occupational Medicine*
Linda Rosenstock, Seattle, Wash

*Ophthalmology*
John L. Keltner, Davis, Calif
Bruce E. Spivey, San Francisco, Calif

*Orthopedics*
George E. Omer, Albuquerque, NM

*Otolaryngology*
Paul H. Ward, Los Angeles, Calif

*Pathology*
Roy I. Davis, Phoenix, Ariz

*Pediatrics*
Roberta A. Ballard, San Francisco, Calif
Allen W. Mathies, Jr, Pasadena, Calif
William D. Robertson, Seattle, Wash

*Pharmacology*
Rubin Bressler, Tucson, Ariz

*Physical Medicine and Rehabilitation*
Julie G. Madorsky, Pomona, Calif

*Plastic Surgery*
Richard P. Jobe, Los Altos, Calif
Henry K. Kawamoto, Jr, Santa Monica, Calif

*Preventive Medicine and Public Health*
Joseph L. Lyon, Salt Lake City, Utah
Jonathan Mann, Geneva, Switz

*Psychiatry*
Ralph Crawshaw, Portland, Ore
Alan I. Levenson, Tucson, Ariz
R. Bruce Sloane, Los Angeles, Calif

*Radiology*
Gary Glazer, Stanford, Calif
Michael L. Manco-Johnson, Denver, Colo
Albert A. Moss, Seattle, Wash

*Surgery*
Haile T. Debas, San Francisco, Calif
Alex G. Little, Las Vegas, Nev
Frank G. Moody, Houston, Tex

*Urology*
Paul H. Lange, Seattle, Wash

*Senior Member at Large*
Edgar Wayburn, San Francisco, Calif

## ADVISORY BOARD, CLINICAL INVESTIGATION

George D. Molnar, Univ of Alberta
Murray A. Katz, Univ of Arizona
Ross E. Petty, Univ of British Columbia
Eldon Shaffer, Univ of Calgary
M. Eric Gershwin, Univ of California, Davis
Jacob Katz, Univ of California, Irvine
Delbert A. Fisher, Univ of California, Los Angeles
Kenneth M. Moser, Univ of California, San Diego
H. Benter Kaltreider, Univ of California, San Francisco
Alan S. Nies, Univ of Colorado
Irwin J. Schatz, Univ of Hawaii
John Peacock, Univ of Nevada
Sanford Schneider, Loma Linda Univ
Kenneth D. Gardner, Jr, Univ of New Mexico
J. David Bristow, Univ of Dregon
Robert M. McAllister, Univ of Southern California
R. Marvin Bala, Univ of Saskatchewan
Allen D. Cooper, Stanford Univ
Gerald Rothstein, Univ of Utah
David R. Saunders, Univ of Washington



## ADVERTISING INFORMATION

Advertising Sales Representatives

EAST/MIDWEST: Cunningham Associates, James C. Cunningham and James Pattis, PO Box 308, Park Ridge, NJ 07656 • (201)767-4170/FAX (201) 767-8065

WEST: Lynne Jeffes, 10 Acacia Lane, Redwood City, CA 94062 • (415) 368-1898

CLASSIFIED: PO Box 7602, San Francisco, CA 94120-7602; overnight mail, 221 Main St, San Francisco, CA 94105 • Tel: (415) 541-0900, ext. 376

*Advertisements*—The journal is published the first week of the month. Advertising copy must be received no later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee. *The journal reserves the right to reject any advertisement.*


## SUBSCRIPTION INFORMATION

The subscription price per year is $30 in the United States and Canada (US funds); $50 in all other countries. Single copies are $5.00. USA/CANADA postage and handling included All other countries add US $4.23 Air Printed Matter Postage. Address all subscription communications to:

THE WESTERN JOURNAL OF MEDICINE Circulation, PO Box 7602
San Francisco, CA 94120-7602 • Tel: (415) 882-5179

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $5.00 is applicable for each issue available.

*Change of Address*—Requests for change of address should give both the old and new address. Allow six weeks for changeover.

## SUBMITTING MANUSCRIPTS

Manuscripts for consideration should be sent to the editor, Linda Hawes Clever, MD, PO Box 7602, San Francisco, CA 94120-7602; overnight mail, 221 Main St, San Francisco, CA 94105.

*"Information for Authors"*—A complete guide to manuscript submission and *WJM* style appears in the January and July issues. Manuscripts may be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (*Annals of Internal Medicine*, Feb 1988; *The Medical Journal of Australia*, Feb 1988).

*Author Responsibility*—Authors are responsible for all statements, conclusions and methods of presenting subjects. Articles are accepted on condition that they are contributed solely to this journal.

*Manuscripts*—Ordinarily manuscripts should not exceed 3,000 words (less than 15 typed double-spaced pages). The *original* manuscript and two copies should be submitted, typed double-spaced throughout. If photographic illustrations are desired, three sets of clear, unmounted black and white glossy prints should be supplied. For line drawings, original artwork or glossy prints are acceptable. Tables should be typed on separate sheets of paper.

*Clinical Investigation*—Papers that authors wish considered for the Clinical Investigation section should be so designated in the transmittal letter. Such papers should describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease.

## PUBLISHER


Copyright 1990 by the California Medical Association • Owned and Published by the California Medical Association.

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with January and July.



***The Western Journal of Medicine***

(ISSN 0093-0415/USPS 084 480) is published monthly for $30 per year (USA and Canada) by the California Medical Association, 221 Main Street, San Francisco, CA 94105. Second-class postage paid at San Francisco and additional mailing offices.

**POSTMASTER:** Send address changes to *The Western Journal of Medicine*, Circulation, PO Box 7602, San Francisco, CA 94120-7602.

# Exceptional Ambulatory Care Facilities . . .

**Casa Blanca Clinic, Ltd.**

**Multi-Specialty Group Practice and Ambulatory Surgery Center**

Sam Davies, Administrator
James Lightner, M.D., Medical Director

SIMMONDS

## The Specialists In Medical Facility Development.

Saint Louis, Missouri ▪ Mercer Island, Washington ▪ Newport Beach, California

206•236•0800

# Investigators' evaluations confirm hair growth in male pattern baldness of the vertex

ROGAINE® Topical Solution (minoxidil 2%) is the *first* prescription medication proved effective for male pattern baldness of the vertex. The effect on frontal baldness has not been adequately studied.

Evidence of growth was demonstrated by physician evaluations of 1,431 patients in 27 centers across the United States. Patients were placed on ROGAINE or placebo and evaluated each month for four months. Response was judged to be no growth, new vellus (baby) hair, or minimal, moderate, or dense growth.

In addition, after the placebo group was discontinued, continuous application of ROGAINE over an additional eight months was evaluated to determine if nonvellus growth could be sustained.

START OF STUDY

START OF STUDY

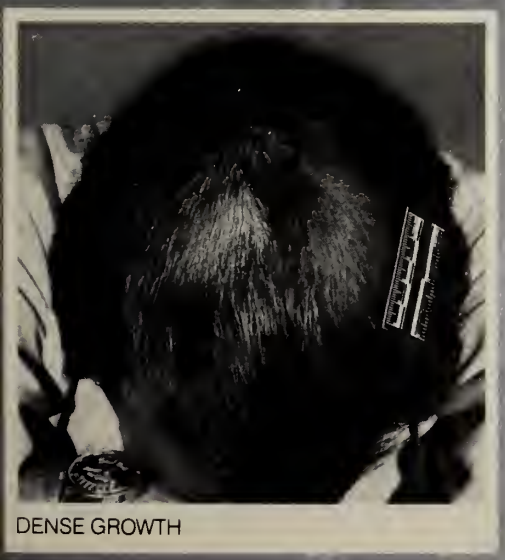
START OF STUDY

Examples of minimal, moderate, and dense growth as evaluated by investigators

© 1989 The Upjohn Company

MINIMAL GROWTH

MODERATE GROWTH

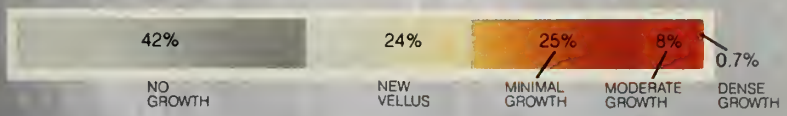


DENSE GROWTH

*Four-Month Phase*

At the end of four months, 34% of 714 patients treated with ROGAINE were evaluated as showing minimal, moderate, or dense growth, while 20% of 717 patients showed minimal, moderate, or dense growth with placebo, a highly significant difference ($P<.0005$).

**Rogaine** (714)




**Placebo** (717)

*Non-Placebo-Controlled Continuation Phase*

After 12 months, dense growth was observed in 8% of the 619 patients treated with ROGAINE, moderate growth in 31%, and minimal growth in 37%. Approximately one fourth of patients showed only vellus hair growth or no growth.

**Rogaine** (619)

*Compliance is Essential*

The multicenter studies indicate that a period of *four months or longer* of daily b.i.d. applications of ROGAINE is usually necessary before evidence of hair growth is apparent. Hair growth continued to increase in study subjects over months 5 through 12.

Continuous use is necessary to maintain hair growth. Newly grown hair returns to the untreated state three to four months after cessation of therapy with ROGAINE.

*Please see last page for brief summary of prescribing information.*

**Rogaine®**
TOPICAL SOLUTION
minoxidil 2%

**Upjohn**

The Upjohn Company
Kalamazoo, MI 49001 USA

# Rogaine® Rx

TOPICAL SOLUTION minoxidil 2%

**INDICATIONS AND USAGE**
Male pattern baldness (alopecia androgenetica) of the vertex of the scalp. No effect has been seen on frontal baldness. At least four months of treatment are generally required before evidence of hair growth can be expected, further growth continues through one year. The new growth is not permanent, cessation of treatment will lead to its loss in a few months.

**CONTRAINDICATIONS**
Hypersensitivity to minoxidil, propylene glycol or ethanol.

**WARNINGS**
*1. Need for normal scalp:* Before starting treatment, make sure that the patient has a normal, healthy scalp. Local abrasion or dermatitis may increase absorption and hence the risk of side effects.
*2. Potential adverse effects.* Although extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects, greater absorption due to misuse, individual variability or unusual sensitivity could, at least theoretically, produce a systemic effect.
Experience with oral minoxidil has shown the following major cardiovascular effects (Review the package insert for LONITEN® Tablets for details):
—salt and water retention, generalized and local edema
—pericardial effusion, pericarditis, tamponade
—tachycardia
—increased incidence of angina or new onset of angina
Patients with underlying heart disease, including coronary artery disease and congestive heart failure, would be at particular risk of these potential effects. Additive effects could also emerge in patients being treated for hypertension.
Potential patients should have a history and physical, should be advised of potential risks and a risk/benefit decision should be made. Heart patients should realize that adverse effects may be especially serious. Alert patients to the possibility of tachycardia and fluid retention, and monitor for increased heart rate, weight gain or other systemic effects.

**PRECAUTIONS**
*General Precautions:* Monitor patients one month after starting ROGAINE and at least every six months afterward. Discontinue ROGAINE if systemic effects occur. The alcohol base will burn and irritate the eye. If ROGAINE reaches sensitive surfaces (eg, eye, abraded skin and mucous membranes) bathe with copious cool water.
Avoid inhaling the spray.
Do not use in conjunction with other topical agents such as corticosteroids, retinoids and petrolatum or agents that enhance percutaneous absorption. ROGAINE is for topical use only. Each mL contains 20 mg minoxidil and accidental ingestion could cause adverse systemic effects.
Decreased integrity of the epidermal barrier caused by inflammation or disease of the skin, eg, excoriations, psoriasis or severe sunburn, may increase minoxidil absorption.
*Patient Information:* A patient information leaflet is included with each package and in the full product information.
*Drug Interactions:* No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine.
*Carcinogenesis, Mutagenesis and Impairment of Fertility:* No carcinogenicity was found with topical application. Oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice. In rats, there was a dose-dependent reduction in conception rate.
*Pregnancy Category C:* ROGAINE should not be used by pregnant women.
*Labor and Delivery:* The effects are not known.
*Nursing Mothers:* ROGAINE should not be administered.
*Pediatric Use:* Safety and effectiveness have not been established under age 18.

**ADVERSE REACTIONS**
ROGAINE was used by 3510 patients in placebo-controlled trials. Except for dermatologic events, no individual reaction or reactions grouped by body systems appeared to be increased in the minoxidil-treated patients.
**Respiratory** (bronchitis, upper respiratory infection, sinusitis) 5.95%, **Dermatologic** (irritant or allergic contact dermatitis) 5.27%, **Gastrointestinal** (diarrhea, nausea, vomiting) 3.42%, **Neurology** (headache, dizziness, faintness, light-headedness) 2.56%, **Musculoskeletal** (fractures, back pain, tendinitis) 2.17%, **Cardiovascular** (edema, chest pain, blood pressure increases/decreases, palpitation, pulse rate increases/decreases) 1.28%, **Allergy** (non-specific allergic reactions, hives, allergic rhinitis, facial swelling and sensitivity) 1.03%, **Special Sense** (conjunctivitis, ear infections, vertigo) 0.94%, **Metabolic-Nutritional** (edema, weight gain) 0.60%, **Urinary Tract** (urinary tract infections, renal calculi, urethritis) 0.46%, **Genital Tract** (prostatitis, epididymitis) 0.46%, **Psychiatric** (anxiety, depression, fatigue) 0.28%, **Hematology** (lymphadenopathy, thrombocytopenia) 0.23%; **Endocrine** 0.09%.
Patients have been followed for up to 5 years and there has been no change in incidence or severity of reported reactions. Additional events reported since marketing include: eczema, hypertrichosis, local erythema, pruritus, dry skin/scalp flaking, sexual dysfunction, visual disturbances including decreased visual acuity, exacerbation of hair loss, alopecia.

**DOSAGE AND ADMINISTRATION**
Hair and scalp should be dry before application. 1 mL should be applied to the total affected areas twice daily. Total daily dose should not exceed 2 mL. If the fingertips are used to facilitate drug application, wash the hands afterwards.

**HOW SUPPLIED**
60 mL bottle with multiple applicators NDC 0009-3367-05
Caution: Federal law prohibits dispensing without a prescription.

B-1-S

**Upjohn**
The Upjohn Company
Kalamazoo, MI 49001 USA

© 1989 The Upjohn Company June 1989 J-9909

# The Great American Food Fight Against Cancer

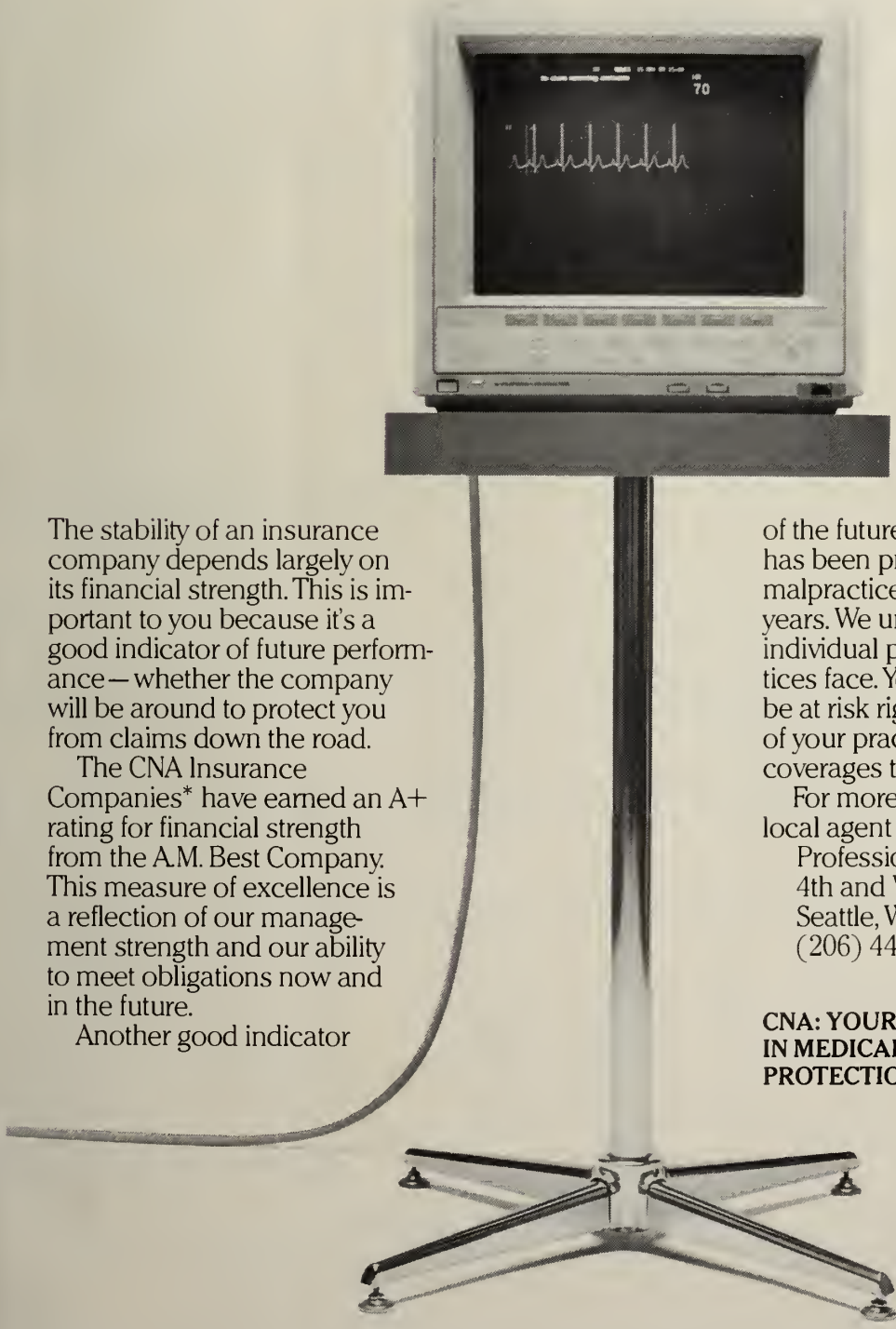
Choose your weapons.

There are surprising new ones in the fight against cancer. Weapons like oranges and squash and bran muffins and brussels sprouts. Because increasing scientific evidence shows that foods that are low in fat and high in Vitamin A and C and fiber may actually reduce your risk of a wide range of life-threatening cancers.

So next time you go to the grocery store, shop to win.

AMERICAN CANCER SOCIETY®

# CNA's financial stability can be vital to the health of your practice.



The stability of an insurance company depends largely on its financial strength. This is important to you because it's a good indicator of future performance—whether the company will be around to protect you from claims down the road.

The CNA Insurance Companies* have earned an A+ rating for financial strength from the A.M. Best Company. This measure of excellence is a reflection of our management strength and our ability to meet obligations now and in the future.

Another good indicator of the future is past performance. CNA has been protecting doctors against malpractice claims for more than 20 years. We understand the special risks individual physicians and group practices face. Your personal assets could be at risk right along with the assets of your practice, and we can tailor coverages to meet your exact needs.

For more information, contact your local agent or:

Professional Insurance Corporation
4th and Vine Bldg.-Suite 200
Seattle, WA 98121
(206) 441-7960

**CNA: YOUR PARTNER IN MEDICAL MALPRACTICE PROTECTION**

*The CNA Physicians Protection Program is underwritten by Continental Casualty Company, one of the CNA Insurance Companies.

**CNA**

**For All the Commitments You Make®**

The Western Journal of Medicine

VOLUME 152 • NUMBER 5 • MAY 1990

# CONTENTS

## ADDICTION MEDICINE

499 **Addiction Medicine**

MALCOLM S. M. WATTS, MD

500 **Addiction Medicine and the Primary Care Physician**

DAVID E. SMITH, MD

*Dr Smith, the guest editor for this issue, is Founder and Medical Director, Haight Ashbury Free Clinics, Inc, San Francisco; Associate Clinical Professor of Occupational Medicine, University of California, San Francisco, School of Medicine; Alternate Delegate, American Medical Association, representing the American Society of Addiction Medicine; and is on the Board of Directors, American Society of Addiction Medicine.*

502 **The New Disease Model of Alcoholism**

JOHN WALLACE, PhD

*From the Department of Community Health, Division of Biology and Medicine, Brown University Program in Medicine, Providence, Rhode Island. Dr Wallace is Director of Treatment, Edgehill Newport, Newport, Rhode Island.*

506 **Chemical Dependency and Drug Testing in the Workplace**

JOHN D. OSTERLOH, MD, and CHARLES E. BECKER, MD

*From the Departments of Laboratory Medicine and Medicine, University of California, San Francisco, School of Medicine, and the Toxicology Laboratories and Divisions of Occupational Medicine and Toxicology, Northern California Occupational Health Center, San Francisco General Medical Center.*

514 **The Role of Physicians as Medical Review Officers in Workplace Drug Testing Programs—In Pursuit of the Last Nanogram**

H. WESTLEY CLARK, MD, JD, MPH

*From the Department of Psychiatry, University of California, San Francisco, School of Medicine, and the Substance Abuse Inpatient Unit, Department of Veterans Affairs, Veterans Administration Medical Center, San Francisco.*

525 **Pulmonary Complications of Smoked Substance Abuse**

DONALD P. TASHKIN, MD

*From the Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of California, Los Angeles, School of Medicine.*

531 **Cognitive Impairments in Abstinent Alcoholics**

GEORGE FEIN, PhD; LEA BACHMAN, PsyD; SARAH FISHER, PhD; and LINDA DAVENPORT, MS

*From the Department of Psychiatry, University of California, San Francisco, School of Medicine, and the Psychiatry Service, Veterans Administration Medical Center, San Francisco.*

538 **Primary Care for AIDS and Chemical Dependence**

LORI D. KARAN, MD

*From the Inpatient Services, Division of Substance Abuse Medicine, Departments of Medicine and Psychiatry, Medical College of Virginia Hospitals, Virginia Commonwealth University, Richmond.*

*(Continued on Page 480)*

*Cover design and illustration by Celeste Rusconi*

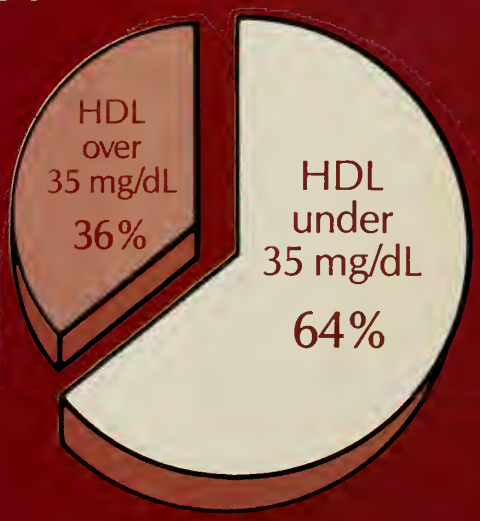
# 240 TOTAL

# <35 HDL

## What's a common denominator of most heart attack victims?

*Mixed* hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] and nearly two thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.[2]

HEART ATTACK PATIENTS (PROCAM TRIAL)[2]




### LOPID raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).[3]

### Reduced heart attack incidence* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).[3]

## A powerful case for

# LOPID®

BID

(gemfibrozil) 600-mg Tablets

RAISES HDL...DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

**References: 1.** Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. **2.** Assmann G, Schulte H. *PROCAM-Trial: Prospective Cardiovascular Münster Trial.* Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis.

Please see adjacent page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

**PARKE-DAVIS**

© 1989 Warner-Lambert Company

**Lopid®** (Gemfibrozil Capsules and Tablets)

**Before prescribing, please see full prescribing information.**
**A Brief Summary follows.**

**CONTRAINDICATIONS.** 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

**WARNINGS.** 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

**PRECAUTIONS.** 1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

**Lopid®** (Gemfibrozil Capsules and Tablets)

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

**ADVERSE REACTIONS.** In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

**Gallbladder surgery** was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

**DOSAGE AND ADMINISTRATION.** The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

**MANAGEMENT OF OVERDOSE.** While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

**References:** 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA. Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

**Caution**—Federal law prohibits dispensing without prescription.

LOPID® BID
(gemfibrozil) 600-mg Tablets
RAISES HDL...DRAMATICALLY
REDUCES HEART ATTACK

**PARKE-DAVIS**
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

0737G013
PD-56-JA-5932-A-1(12-89)

# In Memoriam

## *Arizona Medical Association*

Collings, Robert Z., Casa Grande. Died Feb 25, 1990, aged 78. Graduate of University of Chicago Pritzker School of Medicine, 1939. Licensed in Arizona in 1951. Dr Collings was a member of the Pinal County Medical Society.

Ford, Lattimer H., Phoenix. Died Feb 1, 1990, aged 52. Graduate of State University of New York Buffalo School of Medicine, 1963. Licensed in Arizona in 1969. Dr Ford was a member of the Maricopa County Medical Society.

Giese, Theodore M., Tempe. Died Mar 9, 1990, aged 43. Graduate of Northwestern University Medical School, Chicago, 1972. Licensed in Arizona in 1976. Dr Giese was a member of the Maricopa County Medical Society.

## *California Medical Association*

Amdur, Richard D. Died Jan 4, 1990, aged 61. Graduate of Medizinische Fakultat Der Univ Basel, 1953. Licensed in California in 1955. Dr Amdur was a member of the Los Angeles County Medical Association.

Bethel, Robert D., Pacific Grove. Died Oct 5, 1989, aged 76. Graduate of University of California, San Francisco, School of Medicine, 1942. Licensed in California in 1942. Dr Bethel was a member of the Monterey County Medical Society.

Boggs, Robert W., Burlingame. Died Feb 1990, aged 78. Graduate of Rush Medical College, Chicago, 1938. Licensed in California in 1938. Dr Boggs was a member of the San Mateo County Medical Society.

Brown, Howard A., San Francisco. Died Feb 1990, aged 86. Graduate of University of California, San Francisco, School of Medicine, 1928. Licensed in California in 1928. Dr Brown was a member of the San Francisco Medical Society.

Buck, Lilia, San Francisco. Died Feb 1, 1990, aged 43. Graduate of University of Santo Tomas, Phillipines, 1971. Licensed in California in 1977. Dr Buck was a member of the San Francisco Medical Society.

Campbell, Alice. Died Jul 20, 1989, aged 77. Graduate of Vanderbilt University School of Medicine, Nashville, Tenn, 1937. Licensed in California in 1945. Dr Campbell was a member of the Los Angeles County Medical Association.

Cheung, Joseph. Died Jan 26, 1990, aged 63. Graduate of Faculty of Medicine, University of Hong Kong, 1953. Licensed in California in 1970. Dr Cheung was a member of the Los Angeles County Medical Association.

Clark, Darrel Grant, Santa Paula. Died Feb 25, 1990, aged 91. Graduate of Rush Medical College, Chicago, 1924. Dr Clark was a member of the Ventura County Medical Society.

Clary, Raimond F., Santa Rosa. Died Feb 20, 1990, aged 81. Graduate of Creighton University, Omaha, 1939. Dr Clary was a member of the Sonoma County Medical Association.

Crozier, Henry C. Died Jan 24, 1990, aged 90. Graduate of University of Nebraska, Omaha, 1928. Licensed in California in 1931. Dr Crozier was a member of the Orange County Medical Association.

DeVaul, Charles H., Oakland. Died Feb 12, 1990, aged 100. Graduate of University of Iowa College of Medicine, Iowa City, 1927. Dr DeVaul was a member of the Alameda-Contra Costa Medical Association.

Duncan, Ray Hamilton, St Helena. Died Dec 23, 1989, aged 91. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1941. Licensed in California in 1941. Dr Duncan was a member of the Napa County Medical Society.

Eaton, Charles H., Coronado. Died Jan 18, 1990, aged 74. Graduate of Stanford University, Stanford, California, 1941. Licensed in California in 1941. Dr Eaton was a member of the San Diego County Medical Society.

Flood, Randolph G., San Francisco. Died Oct 9, 1989, age 94. Graduate of Stanford University, Stanford, California, 1922. Licensed in California in 1955. Dr Flood was a member of the San Francisco Medical Society.

Gallup, Charles A. Died Aug 27, 1989, aged 81. Graduate of University of Southern California School of Medicine, Los Angeles, 1937. Licensed in California in 1937. Dr Gallup was a member of the Los Angeles County Medical Association.

Globerson, Irwin. Died Feb 26, 1990, aged 81. Graduate of University of Illinois College of Medicine, Chicago, 1936. Licensed in California in 1940. Dr Globerson was a member of the Los Angeles County Medical Association.

Grant, Sidney. Died Feb 11, 1990, aged 71. Graduate of Medical College of Wisconsin, Milwaukee, 1942. Licensed in California in 1946. Dr Grant was a member of the Los Angeles County Medical Association.

Greer, Edwin D., Arnold. Died Dec 7, 1989, aged 94. Dr Greer was a member of the San Joaquin County Medical Society.

Haasch-Chess, Dorothy Anne, Ventura. Died Jan 2, 1990, aged 74. Graduate of University of Illinois, Chicago, 1947. Licensed in California in 1948. Dr Haasch-Chess was a member of the Ventura County Medical Society.

Harper, Howard E. Died Jan 22, 1990, aged 86. Graduate of George Washington University School of Medicine, Washington, DC, 1934. Dr Harper was a member of the Los Angeles County Medical Association.

Harrington, David O., San Francisco. Died Feb 18, 1990, aged 85. Graduate of University of California, San Francisco, School of Medicine, 1931. Licensed in California in 1934. Dr Harrington was a member of the San Francisco Medical Society.

Hartman, John R., San Luis Obispo. Died Jan 26, 1990, aged 61. Graduate of University of Illinois, Chicago, 1956. Dr Hartman was a member of the San Luis Obispo County Medical Society.

Harwood, David. Died Dec 24, 1989, aged 74. Graduate of University of Toronto Faculty of Medicine, 1939. Licensed in California in 1945. Dr Harwood was a member of the Los Angeles County Medical Association.

Hemminger, George W., Sacramento. Died Sep 15, 1989, aged 83. Graduate of Northwestern University, Chicago, 1931. Dr Hemminger was a member of the Sacramento-El Dorado Medical Society.

Higa, Melvin Tsugio, Merced. Died Dec 5, 1989, aged 35. Graduate of University of California, San Francisco, School of Medicine, 1980. Licensed in California in 1981. Dr Higa was a member of the Merced-Mariposa Medical Society.

Howard, John R. Died Feb 5, 1990, aged 74. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1944. Licensed in Californa in 1944. Dr Howard was a member of the Los Angeles County Medical Association.

Hsu, Chi-Pen, Fresno. Died Feb 3, 1990, aged 56. Graduate of National Defense Medical Center, 1965. Dr Hsu was a member of the Fresno-Madera Medical Society.

Hunt, Irene M. Died Feb 1, 1990, aged 94. Graduate of University of Oregon Medical School, Portland, 1920. Dr Hunt was a member of the Los Angeles County Medical Association.

Husted, Russell M. Died Jul 14, 1989, aged 77. Graduate of University of California, Irvine, California College of Medicine, 1962. Licensed in California in 1975. Dr Husted was a member of the Los Angeles County Medical Association.

Jaekle, Russell, San Francisco. Died Dec 17, 1989, aged 84. Graduate of University of California, San Francisco, 1930. Dr Jaekle was a member of the San Francisco Medical Society.

Jergesen, Floyd H., San Francisco. Died Feb 20, 1990, aged 79. Graduate of Northwestern University, Chicago, 1934. Licensed in California in 1934. Dr Jergesen was a member of the San Francisco Medical Society.

Jones-Soto, Nancy M., San Diego. Died Nov 1989, aged 47. Graduate of Friendship University, Moscow, USSR, 1968. Licensed in California in 1981. Dr Jones-Soto was a member of the San Diego County Medical Society.

*(Continued on Page 485)*

(Continued from Page 476)

543 **Addiction in Adolescents**

MARTHA A. MORRISON, MD

*From Young Adult Services, Anchor Hospital, and the Anchor Recovery Team and Young Adult Services, Talbott Recovery System, Atlanta.*

547 **Drug Abuse, Psychiatric Disorders, and AIDS—Dual and Triple Diagnosis**

STEVEN L. BATKI, MD

*From the Department of Psychiatry, University of California, San Francisco, School of Medicine, and the Substance Abuse Services, San Francisco General Hospital Medical Center.*

553 **The Treatment of Perinatal Addiction—Identification, Intervention, and Advocacy**

MARTY JESSUP, RN, MS

*Ms Jessup is President of the California Advocates for Pregnant Women, Berkeley, California.*

559 **Drug-Exposed Neonates**

GEORGEANNE HOEGERMAN, MD; CATHERINE A. WILSON, MEd; ELLEN THURMOND, LCSW; and SIDNEY H. SCHNOLL, MD, PhD

*From the Departments of Medicine and Psychiatry and the Division of Substance Abuse Medicine, Medical College of Virginia Hospitals, Virginia Commonwealth University, Richmond.*

565 **Drugs of Abuse—Opiates**

WALTER LING, MD, and DONALD R. WESSON, MD

*From the Department of Psychiatry, University of California, Los Angeles, School of Medicine; Los Angeles Drug Abuse Treatment Research Center; and the Department of Psychiatry, University of California, San Francisco, School of Medicine, and Veterans Administration Medical Center, San Francisco.*

573 **Pharmacologic Approaches to the Treatment of Cocaine Dependence**

WANDA A. TAYLOR, MD, and MARK S. GOLD, MD

*From Fair Oaks Hospital, Summit, New Jersey.*

578 **Cigarette Smoking, Nicotine Dependence, and Treatment**

KAREN LEA SEES, DO

*From the Department of Psychiatry, University of California, San Francisco, School of Medicine, and the Substance Abuse Inpatient Unit, Veterans Administration Medical Center, San Francisco.*

585 **Expert Systems in Treating Substance Abuse**

DONALD R. WESSON, MD, and ROBERT H. HINK, PhD

*From the Department of Psychiatry, University of California, San Francisco, School of Medicine, and the Veterans Administration Medical Center, San Francisco, and the Research Department, Merritt Peralta Institute, Oakland, and Expert System Designs, Inc, Berkeley, California.*

588 **Methadone Maintenance in the Treatment of Opioid Dependence—A Current Perspective**

JOAN ELLEN ZWEBEN, PhD, and J. THOMAS PAYTE, MD

*From the 14th Street Clinic and Medical Group, Oakland, California, and Drug Dependence Associates, San Antonio, Texas. Dr Payte is Chair of the Methadone Treatment Committee, American Society of Addiction Medicine, and a Certified Member of the American Society of Addiction Medicine.*

(Continued on Page 486)

# ANNOUNCING A GREAT YEAR AHEAD FOR HERPES PATIENTS

LIFT HERE

## NEW 1-YEAR INDICATION FOR DAILY THERAPY

Herpes patients can look forward to a great year ahead. Results of a recent clinical study show a lesion-free year for nearly half the patients treated with ZOVIRAX Capsules 400 mg b.i.d.[†] [1] For all ZOVIRAX Capsule recipients, recurrences during the study year were limited to a mean of 1.8, compared with a mean of 11.4 for placebo recipients.[1]

Daily use was also shown to be well tolerated. And this extended clinical study demonstrated no evidence of cumulative toxicity and no change in acyclovir sensitivity.[1,2]

Prescribe daily ZOVIRAX Capsule therapy...and help keep your patients lesion-free longer.*

**References: 1.** Mertz GJ, Jones CC, Mills J, et al. Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection: a multicenter double-blind trial. *JAMA.* 1988;260:201-206. **2.** Mertz GJ, Eron L, Kaufman R, et al. Prolonged continuous versus intermittent oral acyclovir treatment in normal adults with frequently recurring genital herpes simplex virus infection. *Am J Med.* 1988;85(suppl 2A):14-19. **3.** Data on file. Burroughs Wellcome Co., 1990.

*In a controlled study of 3 years' duration, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively.[3]

†Alternate maintenance regimens range from 200 mg t.i.d. to 200 mg five times daily.

**ZOVIRAX®**
*(acyclovir)* **capsules**

Please see brief summary of prescribing information on next page.

# ZOVIRAX®
## (acyclovir) capsules

## Daily therapy keeps herpes patients lesion-free longer*

Brief Summary

**INDICATIONS AND USAGE:** Zovirax Capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional and psychosocial difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus Zovirax Capsules are not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories:

**First Episodes** (primary and nonprimary infections—commonly known as initial genital herpes):

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax.

**Recurrent Episodes:**

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that Zovirax Capsules given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients.

In a study of 283 patients who received 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52% and 63% of patients remained free of recurrences in the first, second and third years, respectively. Serial analyses of the 3 month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time.

The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of acyclovir therapy. Re-evaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy. Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year.

Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, Zovirax Capsules should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients with annual re-evaluation.

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

**CONTRAINDICATIONS:** Zovirax Capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

**WARNINGS:** Zovirax Capsules are intended for oral ingestion only

**PRECAUTIONS: General:** Zovirax has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS — Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of Herpes simplex isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of Herpes simplex virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY-Microbiology).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

**Drug Interactions:** Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced. The clinical effects of this combination have not been studied.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg given by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. In 2 *in vitro* cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive life-time bioassays in rodents, conflicting results were obtained. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative in another transformation system considered less sensitive.

In acute studies, there was an increase, not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats but not Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found after 5 days dosing in a dominant lethal study in mice. In 6 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed. At 3 loci in a Chinese hamster ovary cell line, the results were inconclusive. In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells *in vitro*), positive responses for mutagenicity and chromosomal damage occurred, but only at concentrations at least 400 times the acyclovir plasma levels achieved in man.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). At 50 mg/kg/day s.c. in the rat, there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day. No effect upon implantation efficiency was observed when the same dose was administered intravenously. In a rat peri- and postnatal study at 50 mg/kg/day s.c., there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the $F_1$ generation. Although not statistically significant, there was also a dose related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size. However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits, there were no drug-related reproductive effects.

Intraperitoneal doses of 320 or 80 mg/kg/day acyclovir given to rats for 1 and 6 months, respectively, caused testicular atrophy. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. Testicles were normal in dogs given 50 mg/kg/day i.v. for one month.

**Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.) or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures provided plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity. In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation day 10, providing plasma levels 63 and 125 times human levels. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

**Nursing Mothers:** Acyclovir concentrations have been documented in breast milk in two women following oral administration of Zovirax and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when Zovirax is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS—Short-Term Administration:** The most frequent adverse reactions reported during clinical trials of treatment with Zovirax Capsules were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with Zovirax Capsules (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

**Long-Term Administration:** The most frequent adverse reactions reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 Zovirax – treated patients were: nausea (4.8%), diarrhea (2.4%), headache (1.9%) and rash (1.7%). The 589 control patients receiving intermittent treatment of recurrences with Zovirax for 1 year reported diarrhea (2.7%), nausea (2.4%), headache (2.2%) and rash (1.5%).

The most frequent adverse reactions reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%) and paresthesia (0.8%). Reactions reported by 329 patients during the third year include asthenia (1.2%), paresthesia (1.2%) and headache (0.9%).

**DOSAGE AND ADMINISTRATION: Treatment of initial genital herpes:** 200 mg every 4 hours, 5 times daily for 10 days.

**Chronic suppressive therapy for recurrent disease:** 400 mg 2 times daily for up to 12 months, followed by re-evaluation. See INDICATIONS AND USAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

**Intermittent Therapy:** 200 mg every 4 hours, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

**Patients With Acute or Chronic Renal Impairment:** Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment. Based on these studies, a dosage adjustment is recommended for patients with creatinine clearance $\leq 10$ ml/min/1.73 m². For these patients, a 200 mg dose every 12 hours is recommended.

U.S. Patent No. 4199574

*In a controlled study of 3 years' duration, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively.[3]

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

**Burroughs Wellcome Co.,**
Research Triangle Park,
North Carolina 27709

Copr. © 1990 Burroughs Wellcome Co.
All rights reserved ZOC-103 January 1990

# The sun never sets on

## The Western Journal of Medicine


VOLUME 151 • NUMBER 1 JULY 1989

CLINICAL INVESTIGATION

35 Multicenter Trial of Cadexomer Iodine to Treat Venous Stasis Ulcer
G A HOLLOWAY, JR, K H JOHANSEN, R W BARNES, and G E PIERCE

CLINICAL MEDICINE

39 Diagnosing Dislocation of the Hip in Infancy
J H HAZEL and R K BEALS

42 Placebo-Controlled Trial of Quinine Therapy for Nocturnal Leg Cramps
M C FUNG and J H HOLBROOK

CLINICAL REVIEW

45 Review of Pancreatic Trauma
K E GLANCY

CLINICOPATHOLOGIC CONFERENCE

52 Dialysis Disequilibrium Syndrome
C P HARRIS and J J TOWNSEND

MEDICAL STAFF CONFERENCE

56 Therapeutic Options in the Management of Life-Threatening Arrhythmias
Discussants J M HERRE and J C GRIFFIN

EPITOMES

63 Important Advances in Emergency Medicine

EDITORIALS

73 • Medicine in a World of Images and Perceptions
• Pancreatic Injury—A Taxing Problem
• More on the Dialysis Disequilibrium Syndrome

CORRESPONDENCE

83 Low Back Pain Care • Unpredictable Adverse Reactions • Recognizing and Treating Alcoholism • A New Role for American Medicine? • Myositis Due to *Salmonella enteritidis* Bacteremia • Rational Rationing • HRT DOC

SEMINARS IN HEALTH CARE DELIVERY

87 The Hospital Nursing Shortage—A Paradox of Increasing Supply and Increasing Vacancy Rates
L H AIKEN

HEALTH CARE DELIVERY

93 A Peer Review of a Peer Review Organization
S E DIPPE, M M BELL, M A WELLS, W LYONS, and S CLESTER

RADIOLOGIC CASE

97 A 46-Year-Old Woman With a Painless Movable Breast Mass
T MYERS, C J STEGMAN, J K CROWE, and J M LEVY

INFORMATION

99 The Professional Satisfaction of New Mexico Physicians
W S EDWARDS, A G BEZZLER, and S PILT

LESSONS FROM THE PRACTICE

100 Illness as Crime
C T HARRIS

OTHER FEATURES

10 Subscription Information


Most of our readers are in the West, but it is nice to know that THE WESTERN JOURNAL OF MEDICINE is being read around the world—from Australia to the United Kingdom and in countries such as Ecuador, the People's Republic of China, Ethiopia, Brazil, Japan, and Israel.

In addition to reaching far-away places we were chosen by our readers as their most frequently read medical journal—with 35% naming WJM over five key national publications.*

Our name says western, but we are read around the world.

*To subscribe now, please complete the coupon below.*

*The survey was conducted by WJM in March 1989 and sent to 2,790 names picked at random from the WJM readership. The question asked was "How frequently do you read or look into each publication listed"; the journals listed were *Modern Medicine, JAMA, The Western Journal of Medicine, Postgraduate Medicine, Medical Economics,* and *New England Journal of Medicine.* Of those who marked "read frequently" the results were as follows: *The Western Journal of Medicine* (35%), *JAMA* (24%), *New England Journal of Medicine* (21%), *Medical Economics* (12%), *Postgraduate Medicine* (4%), and *Modern Medicine* (4%). For a copy of the study, please call one of our advertising representatives.

## The Western Journal of Medicine

WJ5/90

☐ **1 Year Subscription:** U.S. and Canada $30 • All other countries $50 • Students/Residents (U.S./Canada only) $15

☐ **2 Year Subscription:** U.S. and Canada $50 • All other countries $90

☐ Please bill me ☐ Amount enclosed $ _____ to cover _____ year subscription

☐ Subscription renewal ☐ Regular subscription ☐ Foreign subscription ☐ Student ☐ Resident

TO: _____

Street _____ City _____ State _____ Zip _____

Specialty (If Applicable) _____

Student/Resident Completion Date (Year) _____

Charge my account ☐ VISA ☐ MASTERCARD # _____

Signature _____ Exp. date _____

Subscriptions 12 Issues Per Year • *Please mail this coupon with enclosed payment or give credit card information to:*

Circulation Department • P.O. Box 7602 • San Francisco, California 94120-7602

# SPECIAL ISSUES

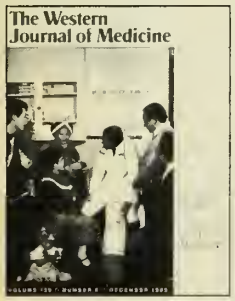
THE WESTERN JOURNAL OF MEDICINE Special May Issue:

MAY 1990

## Addiction Medicine
### and the Primary Care Physician

- OVERVIEW OF ADDICTION MEDICINE *David Smith, Editor/Founder, Haight-Ashbury Free Clinic*
- CHEMICAL DEPENDENCE AND THE WORK PLACE *John Osterloh and Charles Becker*
- THE DISEASE CONCEPT OF ALCOHOLISM *John Wallace*
- COGNITIVE IMPAIRMENTS IN RECOVERING ALCOHOLICS *George Fein*
- SUBSTANCE ABUSE AND PULMONARY PATHOLOGY *Donald Tashkin*
- SPECIAL POPULATIONS: THE ADOLESCENT *Martha Morrison*
- METHADONE MAINTENANCE IN THE TREATMENT OF OPIOID DEPENDENCE *Joan Zweben*
- TREATMENT OF NICOTINE DEPENDENCE IN THE CHEMICALLY DEPENDENT PATIENT *Karen Sees*
- PHARMACOLOGIC APPROACHES TO THE TREATMENT OF COCAINE DEPENDENCE *Wanda A. Taylor and Mark S. G*

## Cross-cultural Medicine




Cross-cultural medicine is devoted to the care of patients of different, cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983. 2nd reprinted edition.

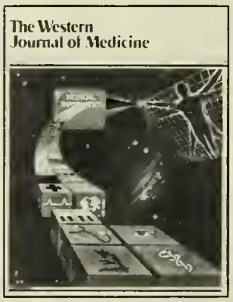
## Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients. Topics covered include liver disease, women and AIDS, heart disease, hysterectomy, PMS, ovarian cancer, and women physicians and organized medicine. Linda Hawes Clever, MD, Special Issue Editor, 1988.

## AIDS—A Global Perspective

This issue, from the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent. Jonathan M. Mann, MD, Special Issue Editor, 1987.

## Medical Informatics




*Medical Informatics* explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

## High-Tech Medicine

This issue examines high-tech medicine as it pertai to patient care. Subjects include lasers i ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ trans plantation, positron emission tomograph and modern molecul biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

---

| Quantity | Per Copy* |
|---|---|
| Single copy | $5.00 |
| 2 to 10 | 4.00 |
| 11 to 50 | 3.50 |
| More than 50 | 3.00 |
| Cross-cultural | 7.50 |
| 50 copies or more | 6.50 |

*Note: USA/Canada postage and handling included, all other countries please add US $4.23 Air Printed Matter postage. Please add California and local sales tax where applicable.

## ORDER FORM

Name _____

Address _____ City/State/Zip _____

Charge my account: ☐ VISA ☐ MASTERCARD

# _____ Exp. date _____

Signature _____

Mail to: Circulation Department, The Western Journal of Medicine
P.O. Box 7602, San Francisco, CA 94120-7602

**Please send me:**

____copies of Addiction Medicine and the Primary Care Physician

____copies of Cross-cultural Medicine

____copies of Women and Medicine

____copies of AIDS—A Global Perspective

____copies of High-Tech Medicine

____copies of Medical Informatics

# In Memoriam

(Continued from page 479)

KLAUMANN, BENJAMIN F. Died Nov 29, 1989, aged 79. Graduate of University of Kansas School of Medicine, Lawrence, 1938. Licensed in California in 1946. Dr Klaumann was a member of the Los Angeles County Medical Association.

❧

MAHER, JOHN A., San Francisco. Died Feb 5, 1990, aged 68. Graduate of Northwestern University, Chicago, 1948. Dr Maher was a member of the San Francisco Medical Society.

❧

MALLARY, CHARLES R., San Francisco. Died Mar 11, 1990, aged 85. Graduate of State University of Iowa, 1931. Dr Mallary was a member of the San Francisco Medical Society.

❧

MARCUS, SIMSON. Died Nov 15, 1989, aged 81. Graduate of University of California, San Francisco, School of Medicine, 1934. Licensed in California in 1934. Dr Marcus was a member of the Los Angeles County Medical Association.

❧

MELINKOFF, EUGENE. Died Dec 23, 1989, aged 75. Graduate of McGill University Faculty of Medicine, Montreal, 1940. Licensed in California in 1940. Dr Melinkoff was a member of the Los Angeles County Medical Association.

❧

MYATT, JOHN P. Died Nov 9, 1989, aged 84. Graduate of University of California, Irvine, California College of Medicine, 1962. Licensed in California in 1975. Dr Myatt was a member of the Los Angeles County Medical Association.

❧

NAESS, ERLING W. Died Dec 12, 1989, aged 79. Graduate of Chicago Medical School, 1940. Licensed in California in 1950. Dr Naess was a member of the Los Angeles County Medical Association.

❧

NORINS, HOWARD. Died Feb 16, 1990, aged 79. Graduate of New York University School of Medicine, 1941. Licensed in California in 1946. Dr Norins was a member of the Los Angeles County Medical Association.

❧

ODEBRECHT, PAUL L., Anaheim. Died Feb 1990, aged 53. Graduate of Western Reserve University, 1963. Licensed in California in 1980. Dr Odebrecht was a member of the Orange County Medical Association.

❧

PETERFY, RICHARD A. Died Jan 28, 1990, aged 81. Graduate of University of California, San Francisco, School of Medicine, 1936. Licensed in California in 1936. Dr Peterfy was a member of the Los Angeles County Medical Association.

❧

READE, FRANK Z., Fullerton. Died Jan 22, 1990, aged 59. Graduate of Creighton University, Omaha, 1961. Licensed in California in 1962. Dr Reade was a member of the Orange County Medical Association.

REYNOLDS, TERRY N., San Bernardino. Died Jan 29, 1990, aged 60. Graduate of St Louis University School of Medicine, 1955. Licensed in California in 1963. Dr Reynolds was a member of the San Bernardino County Medical Society.

❧

ROBINSON, CLINTON W., Healdsburg. Died Jun 4, 1989, aged 71. Graduate of Stanford University, Stanford, California, 1944. Licensed in California in 1944. Dr Robinson was a member of the Sonoma County Medical Association.

❧

ROBSON, PHILIP G., Santa Clara. Died Aug 20, 1989, aged 71. Graduate of Stanford University, Stanford, California, 1944. Licensed in California in 1944. Dr Robson was a member of the Santa Clara County Medical Association.

❧

SALTZER, ARTHUR, Fountain Valley. Died Sep 26, 1989, aged 63. Graduate of University of California, Irvine, California College of Medicine, 1962. Licensed in California in 1975. Dr Saltzer was a member of the Orange County Medical Association.

❧

SCHILLING, MELVIN. Died Oct 14, 1989, aged 73. Graduate of University of California, Irvine, California College of Medicine, 1962. Licensed in California in 1975. Dr Schilling was a member of the Los Angeles County Medical Association.

❧

SMALLBERG, WILLIAM. Died Feb 9, 1990, aged 69. Graduate of University of Texas, 1943. Licensed in California in 1952. Dr Smallberg was a member of the Los Angeles County Medical Association.

❧

STALLONE, VICTOR, JR, Albany. Died Jan 22, 1990, aged 70. Graduate of University of California, San Francisco, School of Medicine, 1944. Dr Stallone was a member of the Alameda-Contra Costa Medical Association.

❧

STEIN, JACK L., Monterey. Died Dec 18, 1989, aged 63. Graduate of Stanford University, Stanford, California, 1950. Licensed in California in 1950. Dr Stein was a member of the Monterey County Medical Society.

❧

STURM, AVERY E., Mariposa. Died Jul 3, 1989, aged 82. Graduate of University of California, San Francisco, School of Medicine, 1934. Licensed in California in 1934. Dr Sturm was a member of the Merced-Mariposa Medical Society.

❧

THORPE, JAMES HANCOCK, San Francisco. Died Dec 23, 1989, aged 61. Graduate of Columbia University College of Physicians and Surgeons, New York, 1953. Licensed in California in 1974. Dr Thorpe was a member of the Marin Medical Society.

❧

TRUMAN, JAMES C., Oakland. Died Dec 1989, aged 57. Graduate of McGill University, Montreal, 1962. Dr Truman was a member of the Alameda-Contra Costa Medical Association.

❧

TUCKER, WILLIAM W., Sacramento. Died Dec 10, 1989, aged 66. Graduate of University of California, San Francisco, School of Medicine, 1946. Licensed in California in 1947. Dr Tucker was a member of the Sacramento-El Dorado Medical Society.

Ads Get Results!

CLASSIFIED ADVERTISING INFORMATION

(415) 541-0900, Ext 376

(Continued from Page 480)

600 **A Physician's Guide to Discontinuing Benzodiazepine Therapy**

ROBERT L. DuPONT, MD

*From the Institute for Behavior and Health, Rockville, Md, and the Department of Psychiatry, Georgetown University School of Medicine, Washington, DC.*

604 **Alprazolam Use and Dependence—A Retrospective Analysis of 30 Cases of Withdrawal**

BILL DICKINSON, DO; PETER A. RUSH, PharmD; and ANTHONY B. RADCLIFFE, MD

*From the Careunit, Ballard Community Hospital, Seattle, and the Chemical Dependence Recovery Program, Kaiser Permanente Hospital, Fontana, California.*

609 **Abuse of Prescription Drugs**

BONNIE B. WILFORD

*From the Department of Substance Abuse, American Medical Association, Chicago.*

613 **Prescription Drug Abuse—Patient, Physician, and Cultural Responsibilities**

DONALD R. WESSON, MD, and DAVID E. SMITH, MD

*From the Departments of Psychiatry and Occupational Medicine, University of California, San Francisco, School of Medicine; the Department of Psychiatry, Veterans Administration Medical Center, San Francisco; the Department of Research, Los Angeles Drug Abuse Treatment Center; the Research Department, Merritt Peralta Institute, Oakland, California; and the Haight-Ashbury Free Clinics, San Francisco.*

617 **Diversion Programs for Impaired Physicians**

RICHARD IKEDA, MD, MPA, and CHET PELTON

*From the Diversion Program, Medical Board of California, Sacramento.*

## OTHER FEATURES

479 **In Memoriam**

483 **Subscription Information**

490 **Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington, Wyoming**

622 **Information for Authors**

628 **Classified Advertising**

642 **Western State Medical Associations' Meetings**

★ **Official Journal of the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.**

★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

*Because safety cannot be taken for granted in $H_2$-antagonist therapy*

# AXID®
## nizatidine

## *Minimal potential for drug interactions*

***Unlike cimetidine and ranitidine,[1] Axid does not inhibit the cytochrome P-450 metabolizing enzyme system.[2]***

## *Swift and effective $H_2$-antagonist therapy*

- *Most patients experience pain relief with the first dose[3]*
- *Heals duodenal ulcer rapidly and effectively[4,5]*
- *Dosage for adults with active duodenal ulcer is 300 mg once nightly (150 mg b.i.d. is also available)*


***References***

1. USP DI Update, September/October 1988, p 120.
2. Br J Clin Pharmacol 1985;20:710-713.
3. Data on file, Lilly Research Laboratories.
4. Scand J Gastroenterol 1987;22(suppl 136):61-70.
5. Am J Gastroenterol 1989;84:769-774.


**AXID®**
nizatidine capsules

**Brief Summary. Consult the package literature for complete information.**

**Indications and Usage:** 1. *Active duodenal ulcer*—for up to eight weeks of treatment. Most patients heal within four weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a reduced dosage of 150 mg h.s. The consequences of therapy with Axid for longer than one year are not known.

**Contraindication:** Known hypersensitivity to the drug. Use with caution in patients with hypersensitivity to other $H_2$-receptor antagonists.

**Precautions:** *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

*Laboratory Tests*—False-positive tests for urobilinogen with Multistix® may occur during therapy.

*Drug Interactions*—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

*Carcinogenesis, Mutagenesis, Impairment of Fertility*—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

*Pregnancy—Teratogenic Effects—Pregnancy Category C*—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Nursing Mothers*—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

*Pediatric Use*—Safety and effectiveness in children have not been established.

*Use in Elderly Patients*—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

**Adverse Reactions:** Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events was due to the drug.

*Hepatic*—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to three times the upper limit of normal, however, did not significantly differ from that in placebo patients. Hepatitis and jaundice have been reported. All abnormalities were reversible after discontinuation of Axid.

*Cardiovascular*—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

*CNS*—Rare cases of reversible mental confusion have been reported.

*Endocrine*—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

*Hematologic*—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another $H_2$-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

*Integumental*—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

*Hypersensitivity*—As with other $H_2$-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Because cross-sensitivity among this class has been observed, $H_2$-receptor antagonists should not be administered to those with a history of hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

*Other*—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

**Overdosage:** Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

PV 2098 AMP [091289]

*Additional information available to the profession on request.*

Lilly

**Eli Lilly and Company**
Indianapolis, Indiana
46285

NZ-2924-B-049310

© 1990, ELI LILLY AND COMPANY

# Command Performances...

## ...Essential to Our Professions

How many times have you felt pressed into a command performance? Whether it's a treatment course or surgery, you feel all eyes are watching your every move. Expectations are high and, oftentimes, unrealistic. Then the unpredictable or the unwanted occurs. Those high expectations are not fulfilled and the next thing you know, you're being sued.

That's why our command performance is so important. When all eyes shift to the legal side, you want an insurance company backing you with excellent claims defense. At ICA, our claims defense is renown in the industry as tough and resourceful. We respond to a claim situation with in-house attorneys, not adjusters. And we use only the best defense counsel in your area, attorneys whose reputations and abilities present the one command performance you'll want to witness.

Call ICA today at 1-(800)-231-2615 and check out the reviews to our command performances.

ICA INSURANCE CORPORATION OF AMERICA
*People Who Care* *Houston, Texas*

# Continuing Medical Education

**ARIZONA • CALIFORNIA, HAWAII, NEVADA • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING**

## ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

May 4—**Infectious Diseases Update: 1990.** Mayo Clinic-Scottsdale. Fri. Contact: Shelia Collins, (602) 391-8300.

May 11-13—**Allergy and Pregnancy Seminar: 1990.** Greater Phoenix Allergy Society at The Registry Resort, Scottsdale. Fri-Sun. Contact: Merle S. Scherr, MD, (602) 994-9514.

May 14-18—**22nd Annual Southwestern School for Behavioral Health Studies.** University of Arizona, Tucson. Mon-Fri. Contact: Susan Villaescusa, (602) 721-3838.

June 22-24—**Thirteenth Annual Pediatrics in the Red Rocks.** American Academy of Pediatrics—Arizona Chapter at Los Abrigados, Sedona. Fri-Sun. Contact: Melanye Wrighton, (602) 230-1949.

### CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

## CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

### ANESTHESIOLOGY

May 17-20—**California Society of Anesthesiologists 1990 Annual Meeting.** California Society of Anesthesiologists at San Francisco Marriott. Thurs-Sun. 18 hrs. $175. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

May 29-June 3—**UCSD Anesthesiology Review Course.** UCSD at San Diego Princess, San Diego. Tues-Sun. Contact: UCSD.

September 8-9—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Lake Tahoe, California. Sat-Sun. 20 hrs. $175. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

October 28-November 2—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Kaanapali Beach, Hawaii. Sun-Fri. 20 hrs. $345. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

### CARDIOLOGY

June 15-16—**Series IV—Cardiac Wellness and Rehabilitation.** Medical Education Resources at Hyatt Union Square, San Francisco. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

June 22-23—**Series I—Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

August 3-4—**Series II—Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Anaheim. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

August 17-18—**Series IV—Cardiac Wellness and Rehabilitation.** Medical Education Resources at Monterey. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

### KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Avenue, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

*(Continued on Page 494)*

# The Last Thing A Small Business Needs Is A Surprise.

## INTRODUCING NO-SURPRISE™ BUSINESS CHECKING. NO PER-CHECK CHARGES, NO OVERDRAFTS.

Once again, Wells Fargo breaks from the pack by introducing business checking with no per-check charges and automatic overdraft protection. No-Surprise Business Checking is especially designed for small business and Wells Fargo is the only major California bank to offer it.

No-Surprise Business Checking means no per-check charges. There's only one flat monthly checking fee, which can be automatically waived by your account balances.

And no more worries about accidental overdrafts. Now you can have automatic protection from your Wells Fargo Business Savings or Market Rate Account.™

New No-Surprise Business Checking. It's only common sense. And it's only at Wells Fargo. To set up your account, talk to a Business Banker™ at your local Wells Fargo office today.

For more information, call 1-800-642-BANK, ext. 504.

Wells Fargo comes through for small business again.

**WELLS FARGO BANK**

©1990, WFB

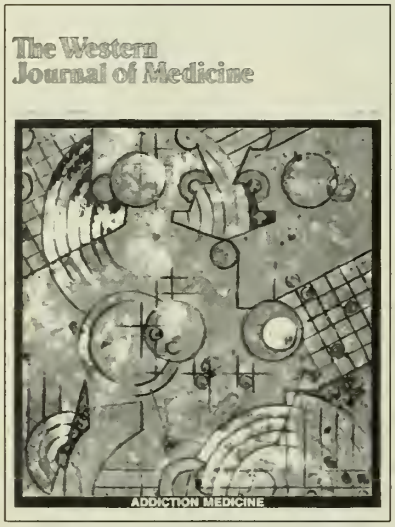
Applies to California residents only.

Member FDIC

A Special Issue of
**The Western Journal of Medicine**

# Addiction Medicine
## and the Primary Care Physician

EDITED BY DAVID SMITH, MD




MAY 1990

- OVERVIEW OF ADDICTION MEDICINE
  *David Smith, Editor/Founder, Haight-Ashbury Free Clinic*
- CHEMICAL DEPENDENCE AND THE WORK PLACE
  *John Osterloh and Charles Becker*
- THE DISEASE CONCEPT OF ALCOHOLISM
  *John Wallace*
- COGNITIVE IMPAIRMENTS IN RECOVERING ALCOHOLICS
  *George Fein et al*
- SUBSTANCE ABUSE AND PULMONARY PATHOLOGY
  *Donald Tashkin*
- SPECIAL POPULATIONS: THE ADOLESCENT
  *Martha Morrison*
- METHADONE MAINTENANCE IN THE TREATMENT OF OPIOID DEPENDENCE *Joan Zweben*
- TREATMENT OF NICOTINE DEPENDENCE IN THE CHEMICALLY DEPENDENT PATIENT *Karen Sees*
- PHARMACOLOGIC APPROACHES TO THE TREATMENT OF COCAINE DEPENDENCE *Wanda A. Taylor and Mark S. Gold*

## ORDER YOUR COPIES NOW!

| Quantity | Per Copy* |
|---|---|
| Single copy | 5.00 |
| 2 to 10 | 4.00 |
| 11 to 50 | 3.50 |
| More than 50 | 3.00 |

*Note: USA/Canada postage and handling included, all other countries please add US $4.23 Air Printed Matter postage. Please add California and local sales tax where applicable.

I would like to order _____ copies of **Addiction Medicine and the Primary Care Physician**

NAME _____

ADDRESS _____

CITY/STATE/ZIP _____

☐ Check enclosed $_____ please charge my ☐ VISA ☐MasterCard

Account #_____ Exp. date _____

Signature _____

Mail to: Circulation Department, *The Western Journal of Medicine*, PO Box 7602, San Francisco, CA 94120-7602

INDEPENDENT SECTOR

Ad Council

# Just a fraction of what we spend on sports can help keep society in shape.

If we all shared just a small part of our extra time and money, society's problems would be no match for us.

Problems like drug abuse. The homeless. Or equal opportunity for all citizens.

Millions of people have helped establish five percent of their incomes and five hours of volunteer time per week as America's standard of giving.

If we all reached this standard, we could generate more than $175 billion every year. With a force equivalent to 20 million full-time workers.

So make it your goal to give five. And help keep society in peak condition.

**Give Five.**

*What you get back is immeasurable.*

CONTINUING MEDICAL EDUCATION

(Continued from Page 490)

## DERMATOLOGY

June 8-9—**Southwestern Regional Cutaneous Flap Workshop.** UCLA. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

June 8-9—**Advances in Skin Cancer Management: A Multi-Specialty Approach.** UCSF at Portman Hotel, San Francisco. Fri-Sat. 10 hrs. $250. Contact: UCSF.

August 3-4—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

August 16-19—**Advanced Seminars in Dermatology.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sun. Contact: UCSD.

## EMERGENCY MEDICINE

May 16-20—**12th Annual: Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

May 27-31—**Annual Scientific Assembly.** California Chapter of the American College of Emergency Physicians at Silverado Country Club, Napa. Sun-Thurs. 18 hrs. Contact: CAL/ACEP, (213) 374-4039.

June 25-29—**Emergency Medicine Symposium III: Pediatrics.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $450. Contact: UCSD.

August 1-5—**Wilderness Medicine: '90.** American College of Emergency Physicians at Squaw Valley Lake Tahoe, Nevada. Wed-Sun. 22 hrs. $395. Contact: Eugene Allred, MD, PO Box 321, Yreka 96097. (800) 888-5632.

August 20-24—**Emergency Medicine Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 11-13—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Hyatt Union Square. Thurs-Sat. 15 hrs. $375. Contact: UCSF.

October 22-26—**Postgraduate Institute for Primary Care and Emergency Physicians Symposium I: Cardiology, Pulmonary, Neurology.** Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 29-November 3—**Topics in Emergency Medicine.** UCSF at Holiday Inn Golden Gate. Mon-Sat. 32 hrs. $460. Contact: UCSF.

## FAMILY PRACTICE/PRIMARY CARE

June 3-8—**14th Annual Fingers to the Toes: Primary Care Orthopaedics.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. 32 hrs. $490. Contact: UCD.

June 11-15—**UCI Family Practice Refresher Course.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. Mon-Fri. 29 hrs. Contact: UCI.

June 27—**AIDS Update for Primary Care: New Hope in a New Era.** Alta Bates-Herrick Hospital at Hospital Auditorium. Wed. 7 hrs. $115. Contact: Mary Grimm, Medical Education Coordinator, (415) 540-1420.

July 9-12—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Thurs. 25 hrs. Contact: UCSF.

July 19-21—**Rheumatology and Arthritis: A Conference for Primary Care Physicians.** Sharp Memorial Hospital at Catamaran Resort Hotel, San Diego. Thurs-Sat. 13 hrs. $250. Contact: Sharp Memorial Hospital, 7901 Frost St, San Diego 92123. (619) 541-3525.

October 3-5—**Primary Care Medicine: Principles and Practice.** UCSF at Holiday Inn Golden Gateway, San Francisco. Wed-Fri. 19 hrs. $425. Contact: UCSF.

## INTERNAL MEDICINE

May 14-18—**Hyperbaric Medicine.** UCI/Memorial Medical Center. 30 hrs. $650. Contact: Celia Loney, (213) 595-3613.

May 18-20—**8th Symposium on Frontiers of Rheumatology.** Annenberg Center for Health Sciences. Fri-Sun. Contact: ACHS, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 321-3690.

June 11-15—**Advances in Internal Medicine.** UCSF at San Francisco Marriott Hotel. Mon-Fri. 33 hrs. $535. Contact: UCSF.

June 25-30—**Advances in Internal Medicine.** UCSF at Cole Hall, San Francisco. Tues-Sat. 32 hrs. $535. Contact: UCSF.

August 19-24—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. Contact: UCD.

September 14-16—**Gastroenterology.** UCSF at San Francisco Hilton and Towers. Fri-Sun. 17 hrs. $415. Contact: UCSF.

October 18-20—**Breast Cancer Seminar.** Memorial/UCI Center for Health Education at Stouffer Hotel, Palm Springs. Thurs-Sat. Contact: UCI.

## OB/GYN

June 1-3—**Advanced Fetal Heart Rate Monitoring.** UCI at Monterey Plaza Hotel. Fri-Sun. Contact: UCI.

June 8-10—**Perinatal High Tech: A Brave New World.** Perinatal Advisory Council of Los Angeles at Fess Parker's Red Lion Resort, Santa Barbara. Fri-Sun. 16 hrs. $150. Contact: Marianne Gray, 3600 Wilshire Blvd, Ste 600, Los Angeles 90010. (213) 380-1790.

August 17-19—**3rd Annual Perinatal Review.** Memorial/UCI Center for Health Education at Four Seasons Hotel, Newport Beach. Fri-Sun. Contact: UCI.

August 21-25—**8th Annual Controversies in OB/GYN.** Memorial/UCI Center for Health Education at Mauna Kea, Hawaii. Tues-Sat. Contact: UCI.

## OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

May 31-June 1—**Occupational and Environmental Medicine.** UCD at Capitol Plaza Holiday Inn, Sacramento. Fri-Sat. 17 hrs. $135. Contact: UCD.

July 23-27—**4th Annual Sports Medicine.** UCSD at San Diego Princess. Mon-Fri. Contact: UCSD.

October 2-7—**Sports Medicine Update.** Memorial/UCI Center for Health Education at Mauna Kea Hotel, Hawaii. Tues-Sun. Contact: UCI.

October 8-19—**Occupational and Environmental Medicine Session II.** UCSF at Cathedral Hill Hotel, San Francisco. 1½ weeks. 80 hours. $1,200. Contact: UCSF.

October 15-19—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

## OPHTHALMOLOGY

May 25-28—**California Association of Ophthalmology: 9th Annual Educational Conference.** California Association of Ophthalmology at Doubletree Hotel Fisherman's Wharf, Monterey Conference Center. Fri-Mon. 6 hrs. $275. Contact: CAO, 605 Market St, Ste 1109, San Francisco 94105. (415) 777-3937.

August 26-30—**Ophthalmology Update: 1990.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

May 11-12—**Visions in Ophthalmology '90.** Scripps Memorial Hospital at La Jolla Marriott. Fri-Sat. 9 hrs. $150. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

## ORTHOPAEDICS

October 4-6—**Orthopaedic Update.** UCSD at Hyatt La Jolla. Thurs-Sat. Contact: UCSD.

## PATHOLOGY

May 24-25—**Current Issues in Anatomic Pathology: 1990.** UCSF at Union Square Holiday Inn, San Francisco. Thurs-Fri. 12 hrs. $300. Contact: UCSF.

(Continued on Page 496)

# What we've done for you lately.

We've taken some concrete steps toward making the less exciting parts of your job less of a problem.

Here's what we did.

We developed ways to speed up claims processing and payments. So you can spend more time worrying about patients, and less time worrying about paperwork.

Our new One Call system helps speed up utilization review and preauthorization. So you can get immediate answers to your benefit and eligibility questions with just one call.

And without being transferred or put on hold.

We've also developed a program called Claim Free™, which further expedites the reimbursement process by eliminating paper claims for both you and your Medicare subscribers.

We're continuing to make these changes for one simple reason: The whole point of health care is to take care of people.

And, by taking better care of you, we're doing just that.

**Blue Cross of California**

We care about what's good for you.

CONTINUING MEDICAL EDUCATION

(Continued from Page 494)

May 26—**Fine Needle Aspiration Tutorials.** UCSF. Sat. 7 hrs. $550. Contact: UCSF.

October 4-6—**International Symposium on Medical Virology.** UCI at Four Seasons Hotel, Newport Beach. Thurs-Sat. Contact: Luis M. de la Maza, (714) 634-6868.

October 12-14—**8th Postgraduate Course in Medical Mycology (Dermatomycology).** UCSF. Fri-Sun. 16 hrs. Contact: UCSF.

October 19—**Fine Needle Aspiration Tutorials.** UCSF. Fri. 7 hrs. Contact: UCSF.

## PEDIATRICS

May 17-19—**23rd Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 16 hrs. $300. Contact: UCSF.

June 29-30—**Current Concepts in Pediatric Allergy and Otolaryngology.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sat. Contact: Continuing Medical Education Office, Children's Hospital, (619) 576-4072.

September 7-8—**Pediatrics and Environmental Health: The Pediatrician as Investigator, Educator, and Advocate.** Children's Hospital Oakland at Berkeley Conference Center. Fri-Sat. 12 hrs. $85. Contact: Joy Carlson, EPI Training Project, 5900 Hollis St, No. E, Emeryville 94608. (415) 540-3657.

October 7-14—**15th Annual Pediatrics for the Practitioner.** Memorial/UCI Center for Health Education at Mauna Kea Hotel, Hawaii. 1 week. Contact: UCI.

## PREVENTIVE MEDICINE

June 3—**Therapeutic Frontiers.** UCLA at Miramar Sheraton Hotel, Santa Monica. Sun. 6 hrs. $50. Contact: UCLA.

## PSYCHIATRY

May 19—**Ideomotor Techniques in Hypnotherapy.** Southern California Society of Clinical Hypnosis at UCLA Neuropsychiatric Institute, Los Angeles. Sat. 5 hrs. Contact: Karnie Starrett, 10840 Queensland St, Los Angeles 90034. (213) 475-1260.

June 8-9—**The Threat to the Cosmic Order: Psychological, Social, and Health Implications of Richard Wagner's Ring of the Nibelung.** UCSF at Laurel Heights Campus, San Francisco. Fri-Sat. Contact: UCSF.

## RADIOLOGY

May 22-25—**CT and MRI in Body Imaging: A Comprehensive Course.** Tues-Fri. 15 hrs. $515. Contact: UCSF.

June 12-16—**Computer Assisted Radiology.** UCI at Anaheim Hilton Hotel. Tues-Sat. Contact: UCI.

July 22-26—**Napa Valley Imaging Update: MRI 1990.** UCD at Silverado Country Club, Napa. Sun-Thurs. 17 hrs. $445. Contact: UCD.

July 23-25—**Musculoskeletal Imaging.** Hoag Memorial Hospital, Department of Radiology at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Wed. 15 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 26-29—**4th Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital, Department of Radiology at Ritz-Carlton Resort Hotel, Laguna Niguel. Thurs-Sun. 22 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 18-19—**Intravascular Ultrasound Imaging.** Memorial/UCI Center for Health Education at Anaheim Hilton Hotel. Sat-Sun. Contact: UCI.

August 23-28—**6th Annual Physics and Biology of Radiology.** UCSD at Hanalei Hotel, San Diego. Thurs-Tues. 25 hrs. $395. Contact: UCSD.

September 7-10—**6th Annual Sonography Update for Physicians and Sonographers.** UCSD at Hotel del Coronado, San Diego. Fri-Mon. 18 hrs. $375. Contact: UCSD.

October 6-7—**Ultrasound: 1990.** UCD at Red Lion Inn, Sacramento. Sat-Sun. Contact: UCD.

October 20-21—**Advanced Imaging of the Musculoskeletal System.** UCSD at Hotel del Coronado. Sat-Sun. 12 hrs. $125. Contact: UCSD.

October 22-26—**15th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $300. Contact: UCSD.

October 26-28—**10th Annual Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 18 hrs. $350. Contact: UCSD.

## SURGERY

May 1990-December 1990—**Temporal Bone Surgical Dissection Courses: 1990.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

May 1990-June 1990—**Microsurgery Training Courses.** UCSD at Grossmont Hospital, La Mesa. 40 hrs. $1,125. Contact: UCSD.

May 19—**Prosthetics-Orthotics Course.** UCD at UCD Medical Center, Sacramento. Sat. Contact: UCD.

June 17-22—**Anatomic Basis for Aesthetic Surgery: Hands-On Laboratory Course.** UCD at Hyatt Regency, Sacramento. Sun-Fri. Contact: UCD.

June 21-23—**7th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Medical Center at La Jolla Marriott Hotel. Thurs-Sat. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 598-0080.

June 28-30—**Contemporary Concepts in Total Joint Replacement.** Memorial/UCI Center for Health Education at Dana Point Resort. Thurs-Sat. Contact: UCI.

July 17-21—**6th Annual Superficial Anatomy and Cutaneous Surgery.** UCSD at La Jolla Marriott. Tues-Sat. Contact: UCSD.

August 8-11—**Sharp Surgical Review Course.** Sharp Memorial Hospital at Le Meridien Hotel, San Diego. Wed-Sat. 14 hrs. $350. Contact: Sharp Memorial, 7901 Frost St, San Diego 92123. (619) 541-3525.

October 6-8—**Anatomic Basis for Aesthetic Surgery: Hands-On Laboratory Course.** UCD at Hyatt Regency, Davis. Sat-Mon. Contact: UCD.

## OF INTEREST TO ALL PHYSICIANS

June 21-23—**Nevada State Medical Association Annual Meeting.** Nevada State Medical Association at Hyatt Lake Tahoe, Nevada. Thurs-Sat. Contact: Nevada State Medical Association, 3660 Baker Lane, Reno, NV 89509. (702) 825-6788.

July 9-13—**2nd Annual Marine Medicine.** UCSD at San Diego Princess. Mon-Fri. Contact: UCSD.

July 19-22—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 26 hrs. $295. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077. (404) 641-9773.

July 23-27—**4th Annual Sports Medicine.** UCSD at San Diego Princess. Mon-Fri. Contact: UCSD.

# COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

(Continued on Page 624)

# YOCON®
## YOHIMBINE HCl

**Description:** Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

**Action:** Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

**Indications:** Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

**Contraindications:** Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

**Warning:** Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

**Adverse Reactions:** Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

**Dosage and Administration:** Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

**How Supplied:** Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

**References:**


1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.


Rev. 1/85

**AVAILABLE AT PHARMACIES NATIONWIDE**

**PALISADES PHARMACEUTICALS, INC.**
219 County Road
Tenafly, New Jersey 07670
**(201) 569-8502**
**1-800-237-9083**

***TAGAMET® (brand of cimetidine)***

***See complete prescribing information in SK&F LAB CO. literature or PDR. The following is a brief summary.***

***Contraindications:*** *'Tagamet' is contraindicated for patients known to have hypersensitivity to the product.*

***Precautions:*** *Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of 'Tagamet' (brand of cimetidine hydrochloride) Injection by intravenous bolus.*

*Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.*

*Reversible confusional states have been observed on occasion, predominantly in severely ill patients.*

*'Tagamet' has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole. Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when 'Tagamet' is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.*

*However, a crossover study in healthy subjects receiving either 'Tagamet' 300 mg q.i.d. or 800 mg h.s. concomitantly with a 300 mg b.i.d. dosage of theophylline [Theo-Dur®, Key Pharmaceuticals, Inc.] demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. [Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.]*

*In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'.*

*A weak antiandrogenic effect has been demonstrated in animals. In human studies, 'Tagamet' has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity.*

*Pregnancy Category B: Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to 'Tagamet'. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.*

*Lack of experience to date precludes recommending 'Tagamet' for use in children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk.*

***Adverse Reactions:*** *Diarrhea, dizziness, somnolence, headache. Reversible confusional states [e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation], predominantly in severely ill patients, have been reported. Reversible impotence in patients with pathological hypersecretory disorders receiving 'Tagamet', particularly in high doses for at least 12 months, has been reported. The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population. Gynecomastia has been reported in patients treated for one month or longer. Decreased white blood cell counts in 'Tagamet'-treated patients [approximately 1 per 100,000 patients], including agranulocytosis [approximately 3 per million patients], have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia [approximately 3 per million patients] and, very rarely, cases of aplastic anemia have also been reported. Increased serum transaminase has been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving 'Tagamet' has been reported. Increased plasma creatinine has been reported. Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported. Rare cases of bradycardia, tachycardia and A-V heart block have been reported with $H_2$-receptor antagonists. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported rarely. Rare cases of polymyositis have been reported, but no causal relationship has been established. Mild rash and, very rarely, cases of severe generalized skin reactions [e.g., Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma] have been reported with $H_2$-receptor antagonists. Reversible alopecia has been reported very rarely.*

***How Supplied: Tablets:*** *200 mg tablets in bottles of 100; 300 mg tablets in bottles of 100 and Single Unit Packages of 100 [intended for institutional use only]; 400 mg tablets in bottles of 60 and Single Unit Packages of 100 [intended for institutional use only], and 800 mg Tiltab® tablets in bottles of 30 and Single Unit Packages of 100 [intended for institutional use only].*

***Liquid:*** *300 mg/5 mL, in 8 fl oz [237 mL] amber glass bottles and in single-dose units [300 mg/5 mL], in packages of 10 [intended for institutional use only].*

***Injection:***

***Vials:*** *300 mg/2 mL in single-dose vials, in packages of 10 and 30, and in 8 mL multiple-dose vials, in packages of 10 and 25.*

***Prefilled Syringes:*** *300 mg/2 mL in single-dose prefilled disposable syringes.*

***Single-Dose Premixed Plastic Containers:*** *300 mg in 50 mL of 0.9% Sodium Chloride in single-dose plastic containers, in packages of 4 units. No preservative has been added.*

*Exposure of the premixed product to excessive heat should be avoided. It is recommended the product be stored at controlled room temperature. Brief exposure up to 40°C does not adversely affect the premixed product.*

***ADD-Vantage® Vials:*** *300 mg/2 mL in single-dose ADD-Vantage® Vials, in packages of 25.*

*'Tagamet' [brand of cimetidine hydrochloride] Injection premixed in single-dose plastic containers is manufactured for SK&F Lab Co. by Baxter Healthcare Corporation, Deerfield, IL 60015.*

*BRS-TG:L79B* *Date of issuance Apr. 1989*

**SK&F LAB CO.,**
*Cidra, P.R. 00639*
*© SK&F Lab Co., 1989*

3:15 AM

# Another night undisturbed by ulcer pain

**The Promise...** 'Tagamet' helps ulcer patients feel better fast.

**The Proof...** 80% of patients with duodenal ulcer, and 77% with gastric ulcer... even smokers, get pain relief with their first dose of 'Tagamet' 800 mg h.s. That's effectiveness. That's fast relief.

For fast relief, rapid healing, effective prevention of duodenal ulcer recurrence, the longest record of safety and unmatched value, there's nothing like...

Tagamet®
brand of cimetidine

SK&F LAB CO.
Cidra, P.R. 00639
© SK&F Lab Co., 1989

*Before prescribing, please see brief summary of prescribing information on adjacent page.*

Journal of the Arizona Medical Association

ARIZONA MEDICINE

May 1990, VOL. XLVII, No.5

Marshall B. Block, M.D.

# Patient/Physician Bonding

About forty years ago Dr. K. Lorenz demonstrated the importance of close maternal offspring contact during a critical period after birth. Now, a great deal is made about mother and baby "bonding" as it appears that there very well may be a critical period following birth in which the child and mother need to be in intimate contact for "imprinting" to occur. That such behavior can occur in adults with their physician and has not been emphasized. Two personal experiences have brought this possibility to mind.

During a recent visit to Phoenix my parents stayed with us. In the middle of the night my father began to experience some chest discomfort which he interpreted to be angina. Because of his past history he became concerned and awoke my mother. She told him to stop worrying and to go back to sleep. He, however, was not appeased and decided to call his physician in Miami Beach. When I awoke the next morning and came into the kitchen to have my morning cup of coffee, he was sitting at the counter relaying to me what had transpired. I looked at him incredulously and said, "But Dad, I was just down the hall, why didn't you come and get me?" His response was probably predictable but nevertheless revealing. "I didn't want to wake you up!" The same thoughts were revealed several years earlier when I asked my parents to accompany us on a family trip to the Middle East. His response was that, "it's too dangerous to go there, you could get shot!" I responded then by saying, "but Dad, you're almost 80 years old and you are going to die sometime anyhow, why not take your chances and come with us?" His response reinforced what happened during his recent visit. He said, "At least if I get sick at home, my doctors are there!"

There thus appears to be a "bonding" between patients and their physicians which we might not fully appreciate. Although this interaction is being eroded by changes in our health care system, there is still a significant dependence placed upon us by our patients. As much as we want to shift responsibility from ourselves to patients in this "enlightened" period of health care delivery, patients still see us as towers of strength and place a great deal of trust in our decisions. We are perceived as life extenders or at least a place where hopes and desires can be fulfilled. For many of our senior citizens, we are their clergy, their family, their confidante, not just a scientist or a specialist. Although surgeons take on this responsibility every time they invade the body, family practitioners and internists do not recognize the degree of trust and reliance patients place in our hands. Furthermore, I doubt whether we perceive our ministrations as having such a dramatic impact as that of a surgeon replacing someone's heart or removing a tumor. Although patients are becoming more educated and sophisticated as well as more realistic in their expectations, as patients age, they are searching for some stability and hope. Although I suspect they realize the limitations that we have, they do think of us in a different light as they evolve. Heavy bonding does occur when physical infirmities become more critical. I think it is important for us to keep in mind our role in this relationship and try to reassure our patients during many of their self limited illnesses and/or acute exacerbations of chronic problems, much as my father's cardiologist did long distance in the middle of the night.

Marshall B. Block, M.D., Editor

Journal of the Arizona Medical Association

ARIZONA MEDICINE

May 1990, VOL. XLVII, No. 5

*Arizona Medicine* is a socioeconomic and scientific journal published monthly by the Arizona Medical Association, Inc., 810 West Bethany Home Road, Phoenix, Arizona 85013, in conjunction with *The Western Journal of Medicine*. All views and opinions expressed in the articles published herein are the authors' and may or may not reflect those endorsed by the Arizona Medical Association.

(602) 246-8901 in Phoenix
1-800-482-3480 Statewide

Mark Ivey, Jr. M.D.
*President*

Chic Older
*Executive Vice President*

Marshall B. Block, M.D.
*Editor*

Susan Fuchs
*Director of Communications*

Gayle Mueller
*Publishing Coordinator*

Linda N. Brown
*Editorial Assistant*

Please notify publisher at least six weeks prior to change of address and include old and new addresses and a mailing label from most recent copy of *Arizona Medicine*. Include your new postal Zip Code number.

## In This Issue:

- Growth of Micro Campuses in Arizona: The AHEC Experience
- Audits
- Gleanings from ArMA Past
- National Practitioner Data Bank
- Physicians in the News
- New Members
- Classified Ads

# The Benefits of Togetherness

Among the best reasons to be part of a professional organization are (1) people who share the same experience understand the challenges facing each other, and (2) as a group people have the resources to solve mutual problems.

Two programs sponsored by the Arizona Medical Association testify to the truth of that precept. Descriptions follow:

## Coping with Lawsuits

One of the loneliest feelings a physician can experience often materializes with the delivery of malpractice lawsuit papers.

ArMA members do not have to confront the isolating, demoralizing litigation experience alone. Physicians who have personally been through the lawsuit system and ***know*** its pressures and problems have formed a support group to help colleagues facing the same trauma. The Physician Support Committee provides emotional support and technical information to help physicians and their families cope with the litigation process.

Contact physicians throughout the state will refer colleagues facing civil legal action to an appropriate committee member who can:

- *Help the sued physician handle stress --*
- *Provide technical information --*
- *Bolster self-confidence --*

If you would like more information about the program, call any of the following physicians:

**Flagstaff—Gilbert Sechrist, M.D., 774-1811**
**Tucson—William J. Mangold, Jr., M.D., 297-8381**
**Yuma—J. Frank Martin, M.D., 344-1400**
**Phoenix—Joseph W. Hanss, Jr., M.D., 258-3262**

## Information Release Clearinghouse

ArMA regularly receives numerous member inquiries regarding release of patient records under a myriad of circumstances.

A "white paper" dealing with the issue, titled "Complying with Subpoenas for Medical Records," was prepared by ArMA legal counsel and staff and was mailed to all members in an effort to provide basic guidelines for physicians who receive subpoenas or court orders. Guidelines change, however, depending on the nature of the request for release of records. Rules for responding to subpoenas are different from rules for responding to court orders or search warrants, and all are different from the way a physician should respond to an attorney's informal request for information from patient records.

Because so many questions exist regarding release of records relevant to legal actions, the Arizona Medical Association will implement a new program to provide quick answers for its members.

Members who have received subpoenas, court orders, search warrants or other requests for patient records from the legal system, and are not sure how to respond, can obtain free advice as to the proper legal course to follow by calling David Landrith, Director of Membership Services, at ArMA's headquarters, (602) 246-8901 in Phoenix or 1-800-482-3480 toll-free statewide.

If the question cannot immediately be answered by ArMA's staff, ArMA's legal counsel will call within 24 hours and advise the member how to respond to the request to release records. More information on the implementation of this program will be forthcoming in the near future. ■

Recently, MICA conducted a survey of our policyholders to discover what questions they had about medical malpractice insurance. During the next few months, we'll respond to their questions.

# COMMONLY ASKED QUESTIONS ABOUT MEDICAL MALPRACTICE INSURANCE ANSWERED BY MICA

**What is MICA doing to reduce rates?**

Working in conjunction with organized medicine, MICA lobbied for the Periodic Payments Bill, which allows certain medical malpractice awards to be paid in installments rather than in lump sums. After it's passage in September of last year, MICA announced a 5% decrease in premiums for all of our policyholders.

MICA continues to monitor the frequency and severity of claims in our effort to reduce rates. In fact, MICA has received approval from the Department of Insurance to reduce rates by 13.8%, for new and renewal business effective April 1, 1990. Together these decreases will represent an 18.2% reduction in our rates within the last year.

Our efforts to screen out suit prone physicians, to handle claims efficiently and to encourage our policyholders' participation in risk management programs have all been effective as well. Our operating expense ratios are among the lowest in the industry.

We are also working for tort reform. We feel that tort reform is the only long term solution to reducing medical malpractice rates.

**What is MICA doing with its profits?**

MICA is a doctor-owned mutual insurance company. We have no stockholders or investors whose concern is profiting from our operation. Our income, which includes premiums received and investment returns, is used to pay judgments, settle and defend claims and pay expenses. Investment earnings are also used to subsidize premiums thereby reducing our members rates. When appropriate, MICA pays dividends. We also keep funds in surplus so that our policyholders can be secure in the knowledge that MICA is a sound company capable of protecting their long term interests.

MICA hopes the answers to these commonly asked questions will help physicians better understand the complexities of medical malpractice insurance.

As a doctor-owned malpractice carrier – insuring more Arizona physicians than any other company – MICA's mission is to provide professional liability insurance at the lowest actuarially sound rates.

MICA **Mutual Insurance Company of Arizona**

To learn more call MICA: **(602) 956-5276** or Toll Free **(800) 352-0402.**

# Growth of Micro Campuses in Arizona: The AHEC Experience

AHEC in Arizona is now an all-state event. For five years the Arizona Area Health Education Center system has been slowly developing new campuses and adding satellites to those already developed.

On September 9, 1989, the tenth through fourteenth (of fifteen) counties were brought on line through the dedication of the Central Arizona Area Health Education Center (CENAHEC) in Globe. The last remaining AHEC to be started in Arizona -- for the fifteenth county -- will be the Maricopa Area Health Education Center (MAHEC) in Phoenix. The dedication of this Center is scheduled for 1990. Not only are there central offices in Nogales, Yuma, Flagstaff, Globe and Phoenix, but satellite offices may be found from Lake Havasu City to Window Rock. AHEC in Arizona is rapidly becoming a statewide resource.

But what is AHEC? As the name, Area Health Education Center, implies, AHECs are local non-profit corporations, serving a specified geographic area, by providing health education services to health professionals. AHECs are ***not*** health education programs for consumers, although they occasionally sponsor such programs.

What do AHECs do? The Arizona AHEC is typical of the AHEC movement nationally, in that it currently provides the following services:

- off-campus education (medicine, nursing, pharmacy, social work, allied health, etc.);
- Continuing Education for health professionals already in the field;
- Learning Resource System (library and computer) support for both students and health professionals; and
- Minority education opportunities through a program of health career awareness and mentoring.

The Arizona AHEC has, to date, compiled an impressive array of achievements as it extends its "micro campuses" away from the university and throughout the state. Some of these data are as follows:

Since its beginning, in October of 1984, over 768 medical students, residents and nurses, and over 144 pharmacy, social work and other allied health students have participated in clerkships or fieldwork rotations sponsored by the Arizona AHEC Program. These rotations have taken place in over 30 communities and have included students from Northern Arizona University, the University of Arizona, Arizona State University and community colleges throughout the state. During these rotations, which average one to six weeks, students are asked to complete information regarding their interest in practicing in a rural area after graduation.

The AzAHEC health professional continuing education program (CE/CME) has served approximately 10,032 health professionals in 154 CE/CME courses since 1985.

Approximately 48% of these health professionals have been physicians or nurses. A wide range of topics are covered in these courses -- from AIDS education to maternal/child health to mental/behavioral health issues. More than a third of the courses offered are general medical education. Over 10% are professional development courses.

In other activities, AzAHEC has enriched already existing medical rotations and has provided substantial support to continue minority opportunity programs such as the Med-Start Program. Since 1987, when AzAHEC initiated a minority recruitment program, approximately 5,862 children and adolescents throughout the state have participated in the "Hands-On" Health Career Day Program, the Med-Start Program or the Mentor Program.

While Arizona statistics are relatively new, some 35 other states around the country demonstrate the effectiveness of the AHEC program. State legislatures have supported AHECs in states as diverse as Virginia, New Jersey, Massachusetts, Ohio, Colorado, California, South Carolina, Kentucky, Arkansas and Florida.

Heavily funded AHECs, such as those in North and South Carolina, have strong programs of graduate medical education. As the Phoenix campus of the University of Arizona College of Medicine grows, the potential for increased linkages between community hospital-based residents and the University will grow.

The focus on health science education, both undergraduate and graduate, in the case of medicine, is for a single purpose. That is the better distribution of health professionals in the United States. AHECs were developed to address a distributional crisis in health care delivery. That crisis has not gone away, but in states with established AHECs it has been much abated. As Arizona faces an uncertain future with respect to health professional availability in its rural and inner-city areas, the AHEC should be seen as a model of choice.

AHEC works, because each individual AHEC becomes a "micro campus," extending the mission of the universities throughout its service area. The initial building process for AHEC in Arizona is now nearing its final stage. The first AHEC (Southeastern Arizona AHEC) will go off federal funding as of October 1, 1990. Unless the State legislature has picked up support for this program at that time, the AHEC program in Arizona will begin to atrophy. This will be just as two new AHECs (the CENAHEC and MAHEC) are coming on stream with major federal support.

AHEC is too good an idea to lose. The 1990 legislative session will be asked to support this program and to provide transitional funding as federal funds are gradually withdrawn. Dollar for dollar, Arizona could not make a better investment in its health care future.

**Andrew W. Nichols, M.D., M.P.H.**


# WHITE WATER

**$79** Per person plus tax

10 miles with lunch. Great idea for family, staff, and clients.

**461-9494**

***SALT RIVER CANYON WHITE WATER RAFTING***

# Audits

*Myth: I don't have to worry; my practice will never be audited.*

*Fact: Chances are good that a physician's practice will be audited at least once. Understanding and preparing for the audit process will keep your practice healthy and successful!*

## Introduction

Today's article will address the areas of insurance audits, what happens during an audit and what the physician can do to avoid unpleasant audits. We will also discuss situations that may trigger an audit and what can be done to prevent misunderstandings.

Audits by their very nature cause anxiety, stress and worry. However, an audit should be thought of as a positive learning experience since it may reinforce the areas in which the physician is correctly coding his or her services. A physician's office should *always* be prepared for an audit, whether expected or unexpected. This type of preparation will enable your practice to operate efficiently, effectively and, most important, honestly.

## What Happens During an Audit?

Audits may be completed in one of two ways, the first of which is performed as a "surprise" audit (one with little warning). The second type of audit is a regularly scheduled audit (one that may be stipulated in an agreement between physician and insurance company). The most common audit is the "surprise" audit.

Generally, if an insurance company wishes to perform an audit, it will provide a few days' notice so that the physician can prepare records and any other documents necessary for the insurance company to complete its audit. Often, the insurance company will request to review the medical records, billing statements, ledgers, and explanation of benefits.

The audit process is usually completed within a few hours for a single physician practice. Larger practices may require more time. The length of the audit also depends on how prepared the physician is for the audit. Scrambling for medical records during an audit adds to the length of the audit as well as makes the physician's practice look disorganized and questionable.

## Common Reasons for Audits

What physicians don't know may hurt them. Take, for example, Mr. Smith, a patient of Dr. Adams for ten years and a recipient of her professional discounts. One day, Mr. Smith had a problem with his insurance payment. Subsequently, he called his insurance company to check on the reimbursement of his claim from Dr. Adams. During the conversation with his insurance company, it was discovered that Dr. Adams routinely provided Mr. Smith with discounts *without* reflecting them on the billing statement. Consequently, the insurance company placed Dr. Adams' practice in a priority audit status. If it is found that Dr. Adams was practicing improper "fee forgiving," her

*-Continued next page*

*Claire Miller and Joan Miller are President and Chief Financial Officer of SysteMedical Management, Inc., a medical practice management firm located in Mesa, Arizona. They can be reached at (602) 833-4855.*

practice could suffer fines and penalties relative to this type of fraud.

Other common reasons for audits include billing statements which appear unusual, inflated charges, multiple charges for uncomplicated illnesses, and bills that appear to be altered.

### How to Prepare for Audits

Not only should physicians learn the proper methods of coding, pricing and billing, as we have discussed in our previous articles, but they should also develop strong communication between staff and patients. This will help eliminate situations such as Dr. Adams'.

Documentation is vital when completing a patient's chart. Be sure the documentation supports the service(s) provided. Also be sure to document any special financial arrangements between you and the patient. This will help when insurance companies question discounts and professional courtesy write-offs.

If you are not aware of your current practice operations, you may be in for a big surprise. Many physicians leave the management of their practice to someone else, leaving it wide open for billing, coding and pricing errors or even embezzlement. If you cannot find the time to manage your office, call on a consultant who can organize your practice and steer you clear of unpleasant audit situations.

### Never Say Never

Trying to fool the system is the same as asking for an audit. If incorrect billings are sent to an insurance company, always (always) submit a corrected statement. This will help clear you of any wrongdoing. Also, be sure to notify the patient of the corrected billing, as this will help eliminate any misunderstanding.

Always be prepared for an audit. By following the ideas presented in this article, your practice will be on its way to becoming well-prepared for an audit.

### Summary

As we conclude the last in our series of practice management articles, we hope that you have learned valuable information about coding, pricing and billing for your services. Effectively managing your practice means the difference between success and failure. ■


AT LAST!!

*PERSONALIZED* CODING AND REIMBURSEMENT TRAINING!!

SysteMedical Management, Inc. has the answers to your coding questions.

We provide *individualized* medical practice management services:

* In-office CPT Coding and Reimbursement Training * Comprehensive Fee Schedule * Fee Analysis
* Complete Practice Analysis * Billing Policies and Procedures Manual * Superbill Analysis and Development

Included with each of our services is *one year of follow-up at no additional cost!!*

Call today for your *FREE CONSULTATION!!!!!*

SysteMedical Management, Inc. • P.O. Box 1168, Mesa, AZ 85211 • (602) 833-4855

## Gleanings From ArMA Past

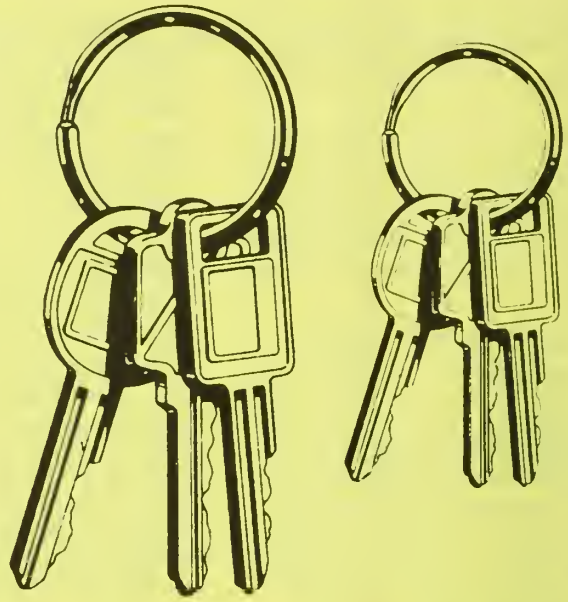
One of Jerome's most colorful characters, **Dr. Woods** lived and practiced in Jerome for a longer period than any of its other doctors. He resided there continuously from 1894 to his death in 1937 at the age of 83.

He was born in Tennessee, but spent his youth in New orleans where be became a driver for and an aide to a doctor. He showed such adaptability that his employer encouraged him to take medical training. He did take a short course in medicine and surgery in a New York elective college.

Woods was an Octoroon and he felt he would find better acceptance away from the south. He came to Arizona. He had not yet become located when in 1892 he found work as a laborer on a freight transfer gang at Jerome Junction. When a workman had a leg crushed in an accident, Woods took charge, amputated the leg and did such a good job of it that H.J. Allen was impressed, brought the young man to Jerome and placed him in charge of the United Verde's new hospital. It was said that Allen had to use his considerable influence in Phoenix to persuade the territorial medical board to issue Woods a certificate to practice, but a few years later Woods was appointed to membership on the board. He remained the United Verde's chief surgeon until 1906. He then set up a private practice which he pursued in a rather desultory way. He was married to Elvia Fazell, a San Francisco opera singer, musician and orchestra conductor of French training. She survived him.

**Dry Gulch Jake**

Reference
Martha Loyel & M.E. Linkert
*Arizona Medicine* XXXIII #6, Page 502



**A good second-hand car.**

An excellent off-lease vehicle can be just the thing to fulfill the need for another car when you don't want a new one. Call your **ArMA** vehicle benefits representative, ***RC Auto Corporation (602) 249-3951.***

**MEDICAL BOOKSTORE**

**MEDICAL BOOKSTORE**
College of Medicine
Arizona Health Sciences Center
Tucson, Arizona 85724
Phone: 626-6669

# National Practitioner Data Bank

*"Its impact on the practicing physician will be far-reaching"*

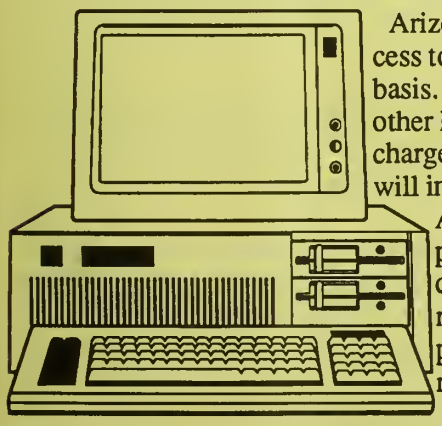
The Federal Government is about to put in place a mandated Physician Tracking Mechanism. There is not an exact date for implementation other than it is expected to go online this summer.

### What Is the Data Bank?

The data bank is an outgrowth of the Health Care Quality Improvement Act (HCQIA) which, among other complex items, provides Congress with a Federal Peer Review System. This mechanism allows for the development of a national system which will act as a depository of malpractice activities and other disciplinary actions taken against physicians and other allied health providers. At the present time it is unclear who, other than physicians, will be targeted "allied health providers."

The system is designed to work with the Board of Medical Examiners and/or other licensing boards. These licensing bodies will be required to submit any actions challenging the doctors competency. Anytime a physician's license is revoked or suspended or in any way restricted, the information will be forwarded to the Data Bank. Additionally, it is supposed that any clinical privileges restricted for more than 30 days will also be reported. The basic premise is that with strict reporting guidelines from licensing boards, hospitals and other health care entities, a comprehensive data base will be maintained on physicians nationwide.

### Access: An Important Concern



Arizona physicians will have access to their files on a "No Charge" basis. Insurance companies and other health care firms will be charged access fees. Access fees will in all likelihood be expensive. A potential problem for physicians will be insurance companies and other entities requesting the physician to pull his/her own file for review.

Hospitals will be required to access the data bank every two years on all physicians having privileges. Hospitals must also query the data bank when physicians apply for clinical or staff privileges. Information about clinical restrictions, censure, probation, or licensing will only be released to firms involved in litigation when there is evidence that the hospital has failed to report or request information as mandated by law. Other health care firms entering into contracts with physicians will in some form or another have access to the physicians' records in the data bank.

### Inaccurate Data and the Consequences

All data will be considered strictly confidential. Employees engaged in processing the data may incur fines up to $10,000 for breach of security. The volume of the data base will be very large. Mechanisms will be put in place that will ensure data integrity for cross referencing. Each physician's personal data ie: home address, social security, date of birth, etc. will be included. This is to ensure that the request for information is the physician in question. All material submitted to the data bank will be held for 30 days before being submitted to interested parties. It is the intent of the data bank to not get involved in disputed claims about the accuracy of information entering the data bank. This has serious ramifications for physicians. Anyone familiar with dealing with credit reporting firms can attest to the difficulty in clearing up disputed or erroneous information. Physicians challenging the information will at least have the option of having the information in question labeled as "disputed status" until such time as they can resolve the matter. Once information arrives at the data bank , the status can only be changed to "revised" thus giving added importance to the original data entry.

### Conclusion

The data bank is coming online. Its impact on the practicing physician and the peer review process will be far-reaching. Arizona physicians need to make themselves aware of the potential impact and to make sure the reporting in peer review is accurate.

**Thomas J. Marks**
**Director,**
**Management Information Services**

# Physicians in the News

The Maricopa County Plastic Surgery Society has elected new officers for the 1990-91 fiscal year. They are **William D. Leighton, M.D.**, Paradise Valley, President; **Andrew M. Wolin, M.D.**, Scottsdale, Vice President; and **Robert J. Spies, M.D.**, Paradise Valley, Secretary-Treasurer.

---

Don W. Hill, M.D.

**Don W. Hill, M.D.**, of Tucson is one of 500 physicians elected to fellowship in the American College of Physicians.

For the past three years Dr. Hill has specialized in internal medicine and medical oncology at Thomas-Davis Medical Center. In 1982 he received his medical degree from the University of Texas Medical School and completed his residency in internal medicine at the University of New Mexico in 1985. He also served a fellowship in medical oncology at the University of New Mexico Cancer Center.

Dr. Hill is the Clinical editorial advisor to the medical publication, *Clinical Hemostasis Review*, published in Denver. He has had several articles published including, "Coagulopathy and Cancer: A Case Report," "Factor XII Deficiency," and "Leukocytosis: A Risk for Thrombosis?"

He is a member of the Southwest Oncology Group, a clinical research group investigating new experimental cancer treatments.

---

Changes in the Soviet Union are impacting international medicine as well. The University of Arizona was among four American institutions selected to be visited by a team of doctors from the National Research Center of Surgery in Moscow. The visiting physicians will spend three months touring these facilities, known for their successful heart transplant programs.

**Jack G. Copeland, M.D.**, heads the Arizona transplant and artificial heart programs at the University. The three visiting heart specialists had witnessed Dr. Copeland perform a transplant on a 48-year-old retired policeman kept alive for 164 days with a Symbion biventricular assist device. The following evening, they saw the patient sitting up and laughing as they stood outside his room in the cardiothoracic intensive care unit.

One of the guests remarked, "It's great, it's fantastic." The visitors said the purpose of their tour is to gather additional knowledge to benefit the relatively inexperienced heart transplant and artificial heart programs in Moscow. The Soviet physicians stated in the past year surgeons at the Moscow institute have performed approximately 35 heart transplants and one heart/lung transplant with about 25 surviving the operations.

According to one of the visiting physicians the trip has helped dispel an old Soviet belief that "the American medical care system (was) money, money, and money."

*(Continued next page)*

# Ahoy Mates! Ahoy!

A "secret desire" became reality for **Alfred F. Miller, M.D.**, when he sailed the Atlantic from Gibralter to Barbados on Tempest, a 46-foot cutter-rigged, heavy displacement fiberglass sailboat.

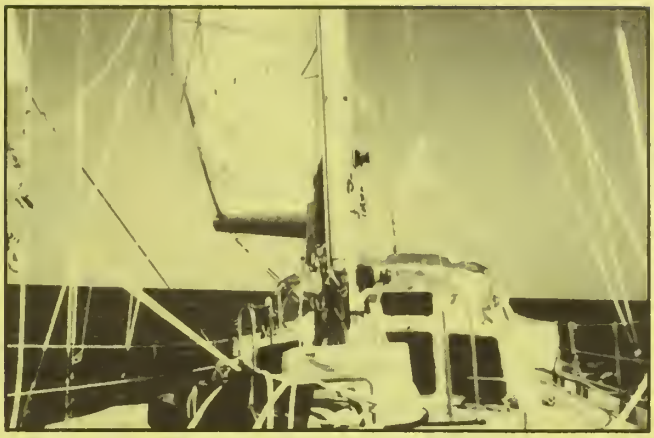
After almost a year of thorough planning, the crew of six (including the skipper) assembled in Gibralter in mid-October 1989. The diverse group along with Dr. Miller, a Phoenix orthopedic surgeon, included the captain, a retired bus system owner from Connecticut; a lawyer from Minnesota; a computer analyst from Connecticut; a special education teacher from New York; and an Episcopal minister and counselor from upstate New York. The crew all had moderate sailing experience.

On October 15 they set sail, traveling 750 miles in six days to the Portuguese island of Madeira. After six days of sightseeing, they continued their trip sailing due south to Gran Canaria, one of the Canary Islands owned by Spain. After thoroughly exploring the island, they left on November 1 to travel the longest leg of the voyage, 2,600 nautical miles to Barbados in the West Indies.

Fortunately they were able to find the world-famed East tradewinds, which enabled them to reach Barbados ahead of schedule in only 16 1/2 days, unusually fast time for a 46-foot vessel. Favorable weather, no big storms, only brief rains, and moderately heavy seas with 10-12 foot waves, added to the enjoyment of this fantastic voyage. They averaged 160 nautical miles daily at a speed of 6 - 6 1/2 knots.

The crew shared equally in standing watches in the cockpit (four hours on, eight hours off), galley duty and boat clean-up. Dr. Miller served as the ship's doctor and fortunately no one had serious medical problems. Ironically, the entire crew was seasick only once, all on the same day.

One of Dr. Miller's biggest thrills was practicing his favorite pastime, celestial navigation, the art of finding one's way across the ocean by sextant sights of sun, moon, planets and stars.



The vessel was well-equipped for transoceanic cruising with single side band and VHF radio, satellite navigation, radar, weather fax, eight-man life raft, fresh water maker, auto pilot, and self-steering wind vane.

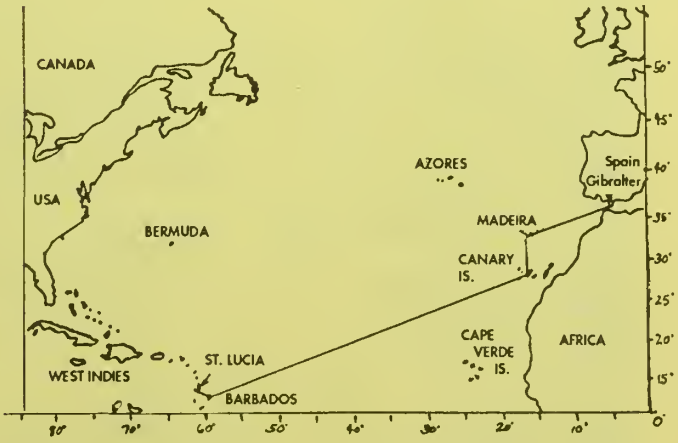
Throughout the trip they were in contact with a North Atlantic ham radio network. Each day they checked in with volunteer network operators who kept a daily log of the vessel's location, destination, weather, etc. If Tempest had failed to report, their previous location would have at least been known.

They followed a common east to west route (see map), but Dr. Miller was amazed that they saw only one freighter and no commercial ships or airplanes the entire Atlantic trip.

After exploring Barbados for three days, Dr. Miller and four of the crew sailed to St. Lucia, a beautiful tropical island 150 miles to the northwest.

The day before Thanksgiving Dr. Miller boarded an airplane back home via Chicago, leaving the delicious Caribbean cuisine, relaxing warm mineral baths and other amenities behind. He landed in a typical midwestern blizzard. Quite a shock after departing only a few hours before from the warm, tropical Caribbean.

"The entire experience was all I had hoped for, and more. I will never forget it," Dr. Miller said with a smile.



# New Members

*Arizona Medical Association welcomes the following new members:*

## *ACTIVE*

### Cochise

**Mari N. Rowe, M.D.**
Family Practice
1101 San Antonio Avenue
Douglas
Rush Medical College
Chicago - 1983

### Maricopa

**John R. Ammon, M.D.**
Anesthesiology
300 W. Berridge Lane, Phoenix
Medical College of Pennsylvania
**Mitchell E. Gibson, M.D.**
Psychiatry, Hypnosis
2600 E. Southern Avenue, #C-3
Tempe
University of North Carolina
School of Medicine - 1985
**Ralph H. Harder, M.D.**
Family Practice
Occupational Medicine
4000 E. Sky Harbor Blvd., Phoenix
Washington University
School of Medicine- 1957
**Ross Levatter, M.D.**
Diagnostic Radiology
Nuclear Medicine
1111 E. McDowell Road, Phoenix
University of Cincinnati
College of Medicine - 1982
**Wendy A. Metzger, M.D.**
Internal Medicine
6301 S. McClintock Dr., Tempe
University of Utah
College of Medicine - 1977
**Gary T. Shaw, M.D.**
Diagnostic Radiology
1301 E. McDowell, #104, Phoenix
University of Arizona
College of Medicine 1983
**Todd B. Taylor, M.D.**
Emergency Medicine
1111 E. McDowell Rd., Phoenix
Indiana University
School of Medicine - 1985
**Stanley M. Wehn, M.D.**
Diagnostic Radiology
5322 W. Northern Avenue, Glendale
University of California San Diego
School of Medicine - 1979

### Pima

**Pamela K. Black, M.D.**
Pediatrics
605 N. Alvernon, Tucson
University of Arkansas
College of Medicine - 1980
**Jessica E. Byron, M.D.**
Obstetrics & Gynecology
2330 N. Rosemont Boulevard
Tucson
Northwestern University
Medical School - 1938
**Michael W. Couch, M.D.**
Emergency Medicine
Family Practice
PO Box 12650, Tucson
Washington University
School of Medicine - 1982
**Michael F. Ginder, D.O.**
Plastic Surgery
4742 N. Oracle Road, Tucson
Philadelphia College of
Osteopathic medicine - 1964
**James MacDonald, M.D.**
Urological Surgery
5402 E. Grant Road, #B-4, Tucson
University of Oregon
School of Medicine - 1983
**Manuel R. Modiano, M.D.**
Oncology, Hematology
1515 N. Campbell Avenue, Tucson
Faculty of Medicine University
Autonoma of Mexico - 1981
**William H. Richardson, M.D.**
Obstetrics & Gynecology
6565 E. Carondelet Drive, Tucson
University of Michigan
Medical School - 1985
**David L. Rogers, M.D.**
Anesthesiology
Arizona Health Sciences Center
Department of Anesthesiology
Tucson
University of Utah
College of Medicine - 1985
**David W. Sundheimer, M.D.**
Internal Medicine
2300 N. Rosemont Boulevard
Tucson
University of North Carolina
School of Medicine - 1986
**Richard D. Tanner, M.D.**
Internal Medicine
6565 E. Carondelet Drive, Tucson
Boston University
School of Medicine - 1978
**Belinda S. Uhall, M.D.**
Internal Medicine
630 N. Alvernon Way, Tucson
University of Arizona
College of Medicine - 1985
**Fred C. Williams, Jr., M.D.**
Neurological Surgery
Arizona Health Sciences Center
Department of Surgery, #4411
Tucson
Baylor College of Medicine - 1983

### Yavapai

**Ronald L. Harvey, M.D.**
Pathology
1003 Willow Creek Road, Prescott
University of New Mexico
School of Medicine - 1970

### Yuma

John R. Sobotka, M.D.
Psychiatry
1952 W. 25th Street, #B
Johns Hopkins University
School of Medicine - 1968

## *RESIDENT*

### Maricopa

**Richard A. Douglas, M.D.**
Neurological Surgery
222 W. Thomas Road, #300
Phoenix
Northwestern University
Medical School - 1983
**Thomas A. Hackenberg, M.D.**
Internal Medicine
Pediatrics
1111 E. McDowell Road, Phoenix
University of North Dakota

School of Medicine - 1988
**David G. Klein, M.D.**
General Surgery
650 E. Indian School Road
Department of Surgery, Phoenix
University of New Mexico
School of Medicine - 1985
**Karen Z. Krishel, M.D.**
Pediatrics
813 W. Madison Street, Phoenix
University of Illinois
College of Medicine - 1986
**Eric J. Pesetsky, M.D.**
Internal Medicine
1111 E. McDowell Road, Phoenix
University of Florida
College of Medicine - 1988
**Jon F. Peters, M.D.**
Family Practice
7301 E. 4th Street, #22, Scottsdale
University of Texas Southwestern
Medical School, Dallas - 1988
**Steven J. Richards, M.D.**
Obstetrics & Gynecology
350 W. Thomas Road, Phoenix
University of Utah
College of Medicine - 1989
**Jeffrey S. Zavala, M.D.**
Family Practice
6025 N. 20th Avenue, Phoenix
University of Colorado
School of Medicine - 1988

### Pima

**Lauri S. Blesch, M.D.**
Pediatrics
1501 N. Campbell Avenue
Department of Pediatrics, Tucson
University of Texas Medical
School, San Antonio - 1987
**Lou L. Lancero, M.D.**
Internal Medicine
Cardiovascular Diseases
PO Box 26926, Tucson
University of California San
Diego School of Medicine - 1982
**Hannah M. Linden, M.D.**
Internal Medicine
Arizona Health Sciences Center
Internal Medicine
Tucson
University of Massachusetts
Medical School - 1989
**Scott V. Slagis, M.D.**
Orthopedic Surgery
Internal Medicine
Arizona Health Sciences Center
Orthopedics, Tucson
University of Southern
California School of Medicine - 1982

## *SERVICE*

### Coconino

**T. Dudley Beck, M.D.**
Family Practice
USPHS Indian Hospital
Tuba City
University of Washington
School of Medicine - 1972

## *ASSOCIATE*

### Maricopa

**Claude E. Forkner, Jr., M.D.**
Internal Medicine
7900 E. Princess Dr. #1016
Scottsdale
Cornell University
Medical College - 1954

### Pima

**Robert B. Bailey, M.D.**
General Practice
135 S. 4th Avenue, Tucson
University of Minnesota
Medical School, minneapolis - 1941

## *STUDENT*

### Pima

**Sheryl D. Galt**
2943B N. Flanwill, Tucson
University of Arizona
College of Medicine (1994)
**Bruce P. Packer**
2145 N. Bell Avenue, #1, Tucson
University of Arizona
College of Medicine (1992)

# Talk to us!

**Have you received special recognition or an award recently from your specialty society or a community organization? Do you know of a colleague who has similarly been honored for medical or community contributions?**

**If so, please let us know. Call Wendy McCullough at ArMA, (602) 246-8901 in Phoenix or 1-800-3480 toll-free statewide. We'd love to share the good news with medical professionals throughout Arizona.**

# PUT YOUR MEDICAL CAREER IN FLIGHT.

Discover the thrill of flying, the end of office overhead and the enjoyment of a general practice as an Air Force flight surgeon. Talk to an Air Force medical program manager about the tremendous benefits of being an Air Force medical officer:

- Quality lifestyle, quality practice
- 30 days vacation with pay per year
- Support of skilled professionals
- Non-contributing retirement plan if qualified

Discover how to take flight as an Air Force flight surgeon. Talk to the Air Force medical team today. Call

USAF Health Professions
Toll Free
1-800-423-USAF

AIR FORCE

# Classified Advertising


**WE WILL BIND YOUR PERIODICALS**

Preserve your medical journals as beautifully bound books. Choose from 24 colors of durable Library Buckram.

**$16.50 Per Volume**
**$20.00 Imitation Leather**
Name imprints (spine) $2.00
Decorative rules $1.00 each

Scattered ad removal $5.00 per volume

Inquire about quantity discounts. Free local pickup and delivery on orders of $250 or more. Minimum order is $35.00.

**ROSWELL BOOKBINDING**
**2614 North 29th Avenue**
**Phoenix, Arizona 85009 ● (602) 272-9338**

PHYSICIAN OFFICE LABORATORY TESTING is on the rise because it leads to increased medical practice efficiency by providing:

- Better patient care
- Increased patient/physician convenience
- Rapid test results for faster diagnosis and treatment

Let ASSOCIATED LABORATORY CONSULTANTS assist you in:

- Reimbursement maximization (proper CPT usage)
- Optimizing your existing laboratory
- Developing a new laboratory

Call 990-0068 for an appointment to discuss your needs.

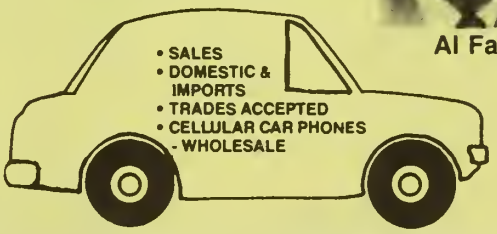
Associated Laboratory Consultants, Inc.,
Scottsdale, Arizona

DANNY T. SEIVERT
INSURANCE, INC.
Professional Programs
for Professional People
70 E. Mitchell Dr., Suite 6
Phoenix, Arizona 85012
263-9090

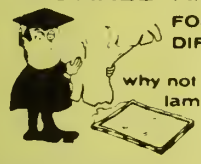
**CONSUMER AUTO BROKERS**
444 W. Camelback, Ste. 203
Phoenix 85013
274-4400

**A Personalized Car Buying Service**

Al Fann




YOU WORKED HARD




it will last a lifetime....

**THE PLAQUE SHOP**

Wood plaques — Ready to hang
No glass to break — Moisture proof
Dirt proof -- Impressive.
Our plaques are manufactured locally

ARIZONA LAMINATING SERVICE, INC.
7231 East First Avenue
Scottsdale, Arizona 85251
(602) 945-9338

## *Professional Opportunities*

### Family Practitioner, BC/BE

To start a comprehensive clinic in Cottonwood, Arizona. Guaranteed salary, plus 50% of all clinic income over and above the salary after expenses, plus malpractice insurance and many other benefits. Contact Josephine Hayes, P.O. Box 421, Cottonwood, AZ 86326, (602) 634-0023.

### Radiologist Practice

Lucrative practice opportunity for radiologist who enjoys rural lifestyle. Excellent hospital, peer association and quality of life. Competitive start up malpractice, relocation reimbursement and more! Please call Lonnie Belden collect at (719) 637-4322 or write to E.G. Todd Associates, 1670 North Newport Road, Suite 300D, Colorado Springs, CO 80916.

### Internist Practice

Lucrative practice opportunity for internist who enjoys rural lifestyle. Excellent hospital, peer association and quality of life. Competitive start up compensation package including an income guarantee, malpractice, relocation reimbursement and more! Please call Lonnie Belden collect at (719) 637-4322 or write to E.G. Todd Associates, 1670 North Newport Road, Suite 300D, Colorado Springs, CO 80916.

### Orthopaedic Practice

If you are interested in a lucrative orthopaedic practice in a well managed, up-to-date hospital, a qualified and supportive medical staff, and a competitive start up compensation package, please call Lonnie Belden collect at (719) 637-4322 or write to E.G. Todd Associates, 1670 North Newport Road, Suite 300D, Colorado Springs, CO 80916.

### Rural Arizona

Five-physician multi-specialty clinic, next to hospital, seeks FP. Year-round recreational activities. Send CV to: Don L. Schatzschneider, Bus. Mgr., Gila Valley Clinic, 2016 W. 16th Street, Safford, AZ 85546 (602) 428-1377.

### Live Among the Redwoods

Successful surgeon seeks partner for busy general and vascular surgery practice on northern California coastline. 85-bed hospital supportive of practice—will provide guarantee and malpractice. Call Gwyneth Anderson for more details about this ideal opportunity at (300) 221-4762, or collect (212) 599-6200. E.G. Todd Associates, 535 Fifth Avenue, Suite 1100, New York, NY 10017.

### Family Practice, Radiology, OB/GYN

Internal Medicine and other specialties needed for small to mid-sized towns in New Mexico and other Sunbelt and Inter-mountain states. Excellent facilities and competitive remuneration packages combine with good schools, outdoor recreation and beautiful locations to provide a quality lifestyle. All inquiries are fully confidential. Call Phyllis or Bruce Moffitt at (505) 898-1114 or send CV to CPS, PO 1163, Corrales, N.M. 87048.

### Board Certified General Surgeon

Wishes to relocate to Arizona. Eight years experience with special interest in diseases of the breast. HMO or hospital based position preferred. Direct inquiries to ArMA, P.O. Box 1990, 810 W. Bethany Home Road, Phoenix, Arizona 85013.

### Phoenix Area

Behavioral Health Program seeking additional adult psychiatrist. Center provides child through adult inpatient, outpatient and partial hospitalization, adult and adolescent CD. Fee-for-services with shared call, or association with existing staff are options. Hospital provides competitive financial support. For more information, call Greg Peterson, E.G. Todd Associates, at (800) 776-7330 or collect (913) 341-7806.

### Locum Tenens Service

Radiologists available for locum tenens or permanent positions. Western Physicians Registry will provide whatever coverage you need for less. Please call Carol Sweig, director, (800) 437-7676.

### Physicians (BC/BE FP or IM)

For unique long-term care program caring for nursing home residents, full or part time. Contact: Medical Director, Long Term Care, Maricopa County, 400 North 7th Street, Phoenix, AZ 85006. (602) 262-8755.

## *Medical Office Space*

### Medical Office Space

1509 sq. ft. built out for doctor in 1987 is now available in Glendale near 53rd Avenue and Northern. Beautiful 1983 Professional Plaza with signage on Northern Avenue. Responsible management. Contact agent: Bill Dutton (602) 241-7916.

### Medical Office

Perfect location—Across from Scottsdale Memorial Hospital-Osborn. Two-office, waiting room and reception. Under $1,000/mo. Call (602) 994-0610.

### Medical Office For Rent

32nd Street near Osborn. 1350 square feet. Ready to move in. $13 per square foot. 3427 N. 32nd St. Call Evelyn. (602)

## *Real Estate*

### Telluride Condo

For sale—3 bedrooms, 2 baths, cathedral ceilings, fully furnished, wood burning stove, walking distance to lift and village. Call (602) 790-6200 — ask for Irma.

## *Miscellaneous*

### Physician Signature Loans

Loans to $50,000. Competitive fixed rates. No collateral. Up to seven years to repay with no pre-payment penalties. Prompt, courteous service. Physicians Service Association, Atlanta, Georgia. (800) 241-6905. Serving MDs for over ten years.

### Retired and Senior Physicians

OMNICARE, a national health care provider is seeking physicians to staff their local clinics. No hassles, remain independent, flexible schedules, and generate extra income. Non invasive, low risk, patient consulting practice. Address all inquiries to John O'Malley, President, 1-800-874-7924.

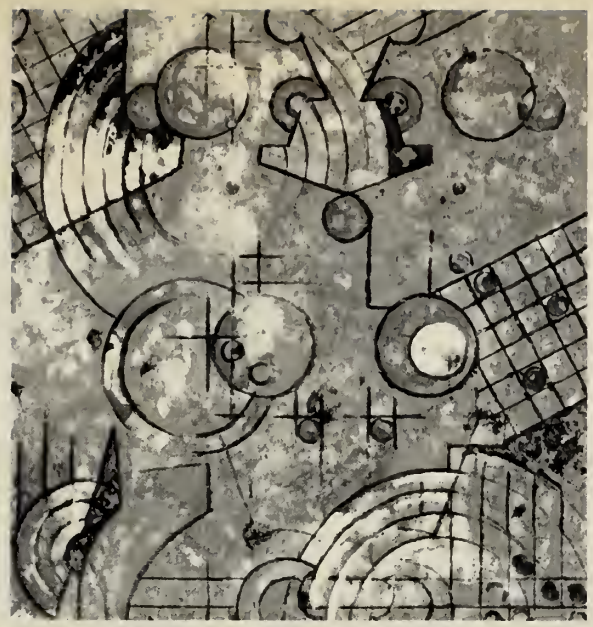
### Large Loans

Since 1966 specializing in large loans to physicians nationwide from $15,000 to $90,000. Long repayment terms at fixed interest rates. Commitments usually within 48 hours. Woodside Capital Corp., Woodside Capital Building, P.O. Box 368, Woodland Hills, CA 91365. For further information, call (800) 423-5025.

### Lab Equipment for Sale

Hemow Cell-counter, Lyte Tek, Coagulation Unimeter 500, Thyrotek. Call (602) 274-6055.

***Classified ads are $20 for the first fifty words and 20 cents for each additional word. Please notify the publishing department at least 6 weeks in advance of any new ads or cancellations.***



# Addiction Medicine

For many years *The Western Journal of Medicine* has had an occasional special issue—usually one each year—on a subject that was deemed at the time to be of growing importance to physicians in medical practice and in their day-to-day care of patients. Previous special issues have addressed clinical nutrition, cost of care, geriatrics, occupational and environmental medicine, cross-cultural medicine, personal health maintenance, high-tech medicine, medical informatics, AIDS from a global perspective, and, most recently, women and medicine. Each topic represented a new major force that, in the opinion of the editors, would influence and change the content or practice of medicine in the years immediately ahead. This year it is clear that chemical dependency and drug addiction are already meeting these criteria. It is also clear that chemical dependency and drug addiction are beginning to affect nearly every physician's practice, yet many physicians, by reason of their training and experience, are not as well-informed about addiction medicine as their practice needs might warrant.

Having decided that a special issue covering various aspects of what is coming to be known as addiction medicine might be informative and useful to our readers, the editors approached Dr David Smith and were able to persuade this very dedicated and very busy physician to be the editor for this special issue on Addiction Medicine. Dr Smith has devoted his professional career to the study and treatment of drug dependency and drug addiction. He founded the Haight Ashbury Free Clinic in 1967 when this district of San Francisco became the gathering place for "flower children" from all over the nation, many of whom soon suffered ill effects from the psychedelic drugs they were wont to use. Although the "flower children" have long since faded, drug abuse has not, and Dr Smith and the Haight Ashbury Free Clinic have continued to be at the cutting edge of our growing experience with what has now become a national and international scourge of drug addiction.

The editors are grateful to Dr Smith and his colleagues for their work in assembling this timely and very special issue on a topic that is beginning to touch almost every physician's life.

MSMW

# Addiction Medicine
## and the Primary Care Physician

Addiction medicine is a medical specialty based on the study and treatment of addictive disease. The American Medical Association (AMA) in June 1987 adopted the resolution that all drug dependencies, including alcoholism, were diseases, and medical practitioners should include in their medical practice an understanding of the different aspects of addictive disease. The American Society of Addiction Medicine, the professional organization representing 3,500 physicians who specialize in addiction medicine, is represented in the AMA House of Delegates, and many states, including California, have state chapters that relate directly to the infrastructure of organized medicine. An expanding number of postdoctoral training fellowships in substance abuse and core curriculum initiatives are designed to improve the quality of undergraduate medical education in this area.

In December 1989 the AMA declared that substance abuse was our country's number one public health problem, with legal drugs such as alcohol and nicotine and illegal drugs such as cocaine and heroin contributing to approximately 25% of all the deaths in the United States each year. In fact, more people die of legal drug addiction than of illicit drug use. Over 350,000 people a year die of the consequences of cigarette addiction and over 100,000 die of alcoholism, whereas the deaths associated with illicit drugs number approximately 20,000 each year. This last figure, however, is increasing, particularly when the correlation between intravenous drug use and AIDS-related deaths is examined, whereas the prevalence of alcohol and nicotine dependence appears to have stabilized.

This issue of THE WESTERN JOURNAL OF MEDICINE, entitled "Addiction Medicine and the Primary Care Physician," is conceptualized as part of the initiative to expand the involvement of all specialties of medicine in the prevention and treatment of addictive disease.

As you read this issue, you will note that the abuse of psychoactive drugs affects every organ system in the body, producing a wide range of signs and symptoms that may in fact mimic other medical and psychiatric disorders. Addiction affects each stage of the life cycle from mother and unborn child through adolescence and middle age to old age. Addiction affects every socioeconomic group including physicians themselves, who in fact may be at an unusually high risk for prescription narcotic addiction self-administered initially in a medical setting. Knowledge of the therapeutic systems available to help chemically dependent physicians is important for identification, intervention, and effective treatment.

Because physicians prescribe potent psychoactive drugs in the practice of medicine that may in fact produce addiction, it is important that they understand the need to vary their prescribing practices with a patient who has a current or past history of addictive disease so that the prescription will be part of the solution rather than part of the problem.

Addiction medicine begins with an understanding of the disease concept. Wallace in his article describes the disease concept of alcoholism, which is the addiction best understood scientifically. Many of his concepts, however, will apply to other addictions as the science of addiction medicine develops. The abuse of alcohol and other drugs produces not only health hazards to our society but also an enormous economic burden. Osterloh and Becker in their article estimate that substance abuse costs industry more than $160 billion per year in lost productivity, health care costs, work-related accidents, and crime. Government has responded to this in part by introducing the Drug-Free Workplace Act parallel with an initiative to expand drug-free screening. Although drug testing of biologic fluid has many established uses, including differential diagnosis, for-cause testing in accident assessment, and monitoring of employees following treatment for addictive disease as they reenter the workplace, random testing raises many technical, clinical, and legal issues for the practicing physician, including the fact that many therapeutic medications may cross-react, producing a positive result on a urine screen designed to detect illicit drug use. Clark in his article describes the critical need for an effective medical review process to ensure accuracy in the drug testing process.

The abuse of psychoactive drugs can affect many different target organ systems, producing pathology and mimicking other disorders. Tashkin in his article notes that a significant number of young cocaine smokers have chest pain and hemoptysis, which are atypical signs and symptoms in that age group unless substance abuse is included in the differential diagnosis. Further, with chronic marijuana use, premalignant pulmonary changes are described, suggesting an increased risk for lung cancer similar to the well-established link between lung cancer and tobacco use.

Information on chronic toxicity such as this is important for the primary care physician in educating young people on the long-term harm of such drugs to prevent their initial or continued use.

Fein and associates describe the prolonged cognitive impairment that alcohol use can produce in the central nervous system. This cognitive impairment may compromise a person's ability to understand health warnings about alcoholism or to participate in certain types of alcoholism treatment unless adjustments for this impairment are made.

Perinatal addiction can have a devastating effect on both mother and child. As with any disease, early identification and intervention are crucial. Hoegerman and colleagues describe the medical and developmental difficulties seen with a neonate with drug exposure. Jessup provides clinical guidelines for the primary care physician and expresses a concern over the growing tendency to criminalize the pregnant addict, which compromises the goal of early intervention.

Drugs that physicians prescribe for therapeutic purposes may also produce dependence. Dupont provides a diagnostic framework for differentiating addiction-prone patients from those seeking therapeutic relief with the most widely prescribed drug group in the United States, the benzodiazepines.

Wesson and Smith provide a broader framework for understanding appropriate prescribing practices for the physician when so much emphasis is being placed on addiction. Most physicians prescribe in a safe and effective fashion, but remedial action needs to be taken for the few who contribute to addiction through inappropriate or outdated prescribing practices.

In the same manner, a minority of physicians themselves become addicted. Ikeda and Pelton describe the program in California available to help chemically dependent physicians. Although each state varies, all have some therapeutic as well as disciplinary system for responding to addicted physicians. The AMA has played a pivotal role in developing a nationwide system of education, prevention, and therapeutic response for physicians who fall victim to this potentially fatal issue of addiction.

The treatment of addictive disease begins with detoxification from drug dependence. In the rapidly changing world of addiction medicine, it is difficult for primary care physicians to keep up with the many new developments in detoxification. Wesson describes new technology to aid the primary care physician in obtaining appropriate, up-to-date information on detoxification.

Other authors discuss AIDS and chemical dependency, treating patients who have both addiction and psychiatric disorders, and pharmacologic approaches to the treatment of opioid, cocaine, and nicotine dependence.

There has been a dramatic increase in knowledge about brain chemistry and addictive disease in the 25 years since I entered the field of addiction medicine. We have a much better understanding of the pathophysiology of addiction, which has set the stage for new pharmacologic interventions. The National Institute on Drug Abuse has a Medications Development Program designed both to encourage the development of new agents for treating addiction and to stimulate public-partnership cooperative efforts to better treat addiction. This issue of the journal contains discussions of several of these new pharmacologic interventions, particularly with cocaine, nicotine, and opioid dependence.

I want to thank Malcolm Watts and Holly Smith for inspiring me to develop this theme issue of THE WESTERN JOURNAL OF MEDICINE. They approached me after I gave an alumni speech at our University of California, San Francisco, 25-year class reunion, which shows that if you stay around long enough, good things happen.

I would also like to thank my colleagues in the American Society of Addiction Medicine for their pioneering work in developing this exciting field.

DAVID E. SMITH, MD

*Special Editor*

*Founder and Medical Director*
*Haight Ashbury Free Clinics, Inc*

*Associate Clinical Professor of Occupational Medicine*
*University of California, San Francisco*

*Alternate Delegate, American Medical Association*
*Representing the American Society of Addiction Medicine*

*Board of Directors*
*American Society of Addiction Medicine*
*San Francisco*

**Addiction Medicine**
**and the Primary Care Physician**

# The New Disease Model of Alcoholism

JOHN WALLACE, PhD, *Newport, Rhode Island*

*The new biopsychosocial disease model of alcoholism is examined from the perspective of recent biologic research. Studies of animal and human genetic predispositions suggest the presence of genetic influences over drinking behavior as well as biologic risk factors related to deficiencies in various neurochemicals. Ethanol affects the fluidity of cell membrane lipids, eventually causing membrane dysfunction. It also adversely affects the activity of two enzymes, monoamine oxidase and adenylate cyclase, that have important functions in the information processing system of the brain. Research on condensation products formed in the brain after alcohol consumption has provided clues to the development of alcoholism, but many questions remain unanswered. Alcoholism is clearly a multidimensional phenomenon in which biologic, psychological, and sociocultural factors interact to produce illness.*

(Wallace J: The new disease model of alcoholism, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:502-505)

In recent years, considerable progress has been made in conceptualizing alcoholism as a disease. This modern disease model is multidimensional and incorporates biologic, psychological, and sociocultural factors. Alcoholism is increasingly being viewed as a biopsychosocial illness in which genetics, neurochemistry, pharmacology, behavior, and social environment are involved.[1-4] In this article I discuss recent work concerning the biologic dimension of the biopsychosocial model of alcoholism.

## Animal Behavioral Genetic Studies

Selective breeding and genetic selection techniques have been used successfully to develop strains of mice and rats that differ in alcohol-related behaviors.[5,6] A preference for alcohol over water and a differential sensitivity to the drug have been shown to be genetically influenced. The C57BL/6 mouse strain shows a tendency to prefer alcohol to water, whereas the DBA/2 strain does not. Another strain, the "short-sleep" mouse, shows considerable resistance to alcohol's effect on the righting reflex while the "long-sleep" mouse appears highly vulnerable to this drug effect.

In studies of short-sleep and long-sleep mice, a 30-fold increase in a dose of alcohol is required to produce the same level of impairment in Purkinje's neurons of short-sleep mice evident in long-sleep mice at much lower doses.

Li and colleagues have developed two strains of rats, the "alcohol-preferring" and "alcohol-nonpreferring" strains.[7] Li points out that for animal models of drinking behavior to have relevance to alcoholism in humans, the following criteria must be met: the animals must seek out alcohol, ingest it orally, engage in efforts to get the drug, develop a tolerance to alcohol, and become physically dependent on it. Li's alcohol-preferring rats show all of these criteria.

Hence, recent studies of animal behavioral genetics indicate that considerable genetic influences on animal drinking behavior exist and enter into alcohol preference and a differential sensitivity to alcohol. Studies of drugs other than alcohol have shown similar results. In fact, for all drugs investigated, significant genetic differences in drug self-administration have been found.[8] Among the opioids, genetic differences in the self-administration of morphine, codeine, and etonitazene have been shown in animals. Genetic differences in cocaine self-administration, locomotor activation, lethality, and the incidence of cocaine-induced seizures have also been found.

## Recent Human Genetic Studies

Human genetic studies are consistent with animal studies in showing genetic influence. Schuckit has found that sons of alcoholic parents appear less sensitive to some psychomotor effects of ethanol than are sons of nonalcoholic parents.[9] Sons of alcoholic parents showed significantly less body sway and differences in hormonal reactions and gave fewer subjective reports of intoxication compared with sons of nonalcoholic parents when both groups received identical amounts of alcohol.

Cloninger and colleagues used adoption-study techniques to investigate genetic influences in etiology.[10] When Swedish adopted children of alcoholic and nonalcoholic parents were studied, substantial genetic influences were shown for two different types of alcoholism. Type I alcoholics showed a later onset of the disease, little or no criminality, and a threefold increased risk for alcoholism and appeared to require an interaction between genetics and environment for the development of the disease.

In type II alcoholics, the disease began early, was associated with considerable criminal behavior, and there was a ninefold increase in the risk for alcoholism. In contrast to type I alcoholics, type II alcoholics did not require environmental factors for the disease to develop. For this particular

From the Department of Community Health, Division of Biology and Medicine, Brown University Program in Medicine, Providence, Rhode Island. Dr Wallace is Director of Treatment, Edgehill Newport, Newport, Rhode Island.

Reprint requests to John Wallace, PhD, Edgehill Newport, 200 Harrison Ave, Newport, RI 02840.

set of empiric observations, genetic factors alone were sufficient to produce the illness in type II alcoholics.

Cloninger's data also pointed to a genetic factor for alcoholism in women. Earlier adoption studies by Goodwin and colleagues in Denmark had shown genetic influence in alcoholism in men but not in women.[11] Goodwin's samples, however, had included few mothers and daughters. Cloninger's samples included a sufficient number of women for the question of genetic influence on alcoholism in women to be considered. When the biologic mothers in Cloninger's study were alcoholics, daughters showed a threefold increase in the incidence of alcoholism. Daughters of biologic alcoholic fathers also showed an increased risk for alcoholism, but not as substantial an increase as seen in biologic mothers and daughters.

## The Search for Biologic Risk Factors

While genetic influence has been demonstrated, the precise nature of genetic risk factors remains unknown. There are promising leads, however. In rats, alcohol preference has been consistently related to deficiencies in serotonergic neurotransmission. Li and associates have shown consistent deficiencies in serotonin in particular brain locations (cerebral cortex, thalamus, hypothalamus, hippocampus, and corpus striatum).

These findings of genetic differences in serotonin are consistent with experimental studies involving increases and decreases in serotonin in animals and humans. When the serotonin level is reduced, ethanol consumption has been shown to increase.[12] Conversely, when the serotonin level is raised, ethanol consumption was found to decrease.[13]

Studies of other neurotransmitters and neuromodulators suggest involvement of other brain chemicals in addition to serotonin. Blum and co-workers have reported an association between enkephalin levels and ethanol preference in mice.[14] Moreover, this relationship between levels of a brain opioid peptide and ethanol consumption appears to be genetically influenced.

In Sweden, Borg and colleagues reported a possible role for noradrenergic neurotransmission in the relapse to active alcoholism among those recovering from alcoholism.[15] Paradoxically, alcoholic persons with *lower* noradrenergic activity three to six months into recovery showed higher rates of relapse.

The search for biologic risk factors in alcoholism is complicated by the considerable heterogeneity apparent in both clinical and nonclinical samples of alcoholics and problem drinkers. It is entirely possible that different biologic types exist and that different groups of risk factors will prove necessary to account for this apparent heterogeneity. Hence, while one type may show problems in serotonergic neurotransmission, another type may show disturbances in dopaminergic neurotransmission. Elsewhere I argue that persons with alcoholism may differ greatly in activation or arousal levels, with one type showing excessive arousal and another type showing levels of arousal so low that they border on outright anhedonia.[16(p9)]

As a consequence, some persons with alcoholism may relapse in response to excessive stimulation, stress, and high arousal-related discomfort whereas others may drink in response to boredom, restlessness, and an inability to experience pleasure. Different types of alcoholism may produce different underlying neurochemical deficits; these, in turn, may be related to different genetic risk factors.

Cloninger's data pointed to the possibility that certain inherited personality characteristics distinguishing type I from type II alcoholics may constitute genetic risk factors. Type I alcoholics are thought by Cloninger to be high in the traits of harm avoidance and reward dependence and low in the trait of novelty seeking. Type II alcoholics are low in the traits of avoiding harm and reward dependence but score high on the measures of the trait of novelty seeking. Cloninger thinks that these genetically influenced differences in personality traits and associated differences in neurochemistry constitute the important genetic risk factors for alcoholism.

## Genetics of Alcoholism: A Summary

I have summarized recent research on genetics and alcoholism as follows:

- Research in genetics has contributed strong evidence in favor of a disease model of alcoholism;
- Various predispositions, risk factors, or vulnerabilities to the disease are inherited, although alcoholism per se does not appear to be;
- These genetic predispositions or risk factors come into play as people consume more and more alcohol;
- Environment must also play a role in causation because not everyone in whom alcoholism develops has a positive family history of the disease;
- In many cases of alcoholism, the roles played by culture and society acting alone or in concert with genetics must be explored;
- Differences between and among various alcoholics may be related to underlying differences in neurochemistry.

## Cell Membrane Research

When large amounts of alcohol are forced into a cell membrane, the fatty bilayers that make up the membrane become even more fluid than they normally are. These disturbances of the cell wall fluidity by alcohol are thought by some to be the biologic basis of intoxication. In adapting to this increased fluidity, the cell stiffens. This stiffening of the cell wall is thought to be the biologic basis of tolerance to alcohol ("tolerance" refers to the need for larger doses of a drug to get the same effect). Finally, as a person drinks larger and larger quantities of alcohol, the cell wall becomes rigid. At this point the cell membrane becomes hyperexcitable and the person is in danger of having a seizure. It has been hypothesized that rigid cell membranes in the brain are the biologic basis of physical dependence.[17]

Some researchers argue that alcohol acts directly on the large protein molecules embedded in the lipid bilayers of cell membranes and that it is these direct actions on proteins that are important, rather than the changes taking place in the fatty bilayers of the membranes.[18]

Whether alcohol's most important effects are on the lipids making up the cell wall or on the proteins embedded in these lipids is a highly technical question that can only be resolved by further research. The implication here seems clear, however. Alcohol is a drug that can and does affect major brain structures and processes. These changes in the brain that occur with heavy drinking are what is meant, in part, when it is said that alcoholism is a disease.

### Monoamine Oxidase and Adenylate Cyclase

Recent research has also looked at certain enzymes involved in the brain's information-processing system. Monoamine oxidase and adenylate cyclase are two important enzymes. Monoamine oxidase is important because it is crucial to the metabolism and turnover of the neurotransmitters dopamine, noradrenaline, and serotonin. A deficiency in monoamine oxidase or a decrease in its activity results in problems in brain function.

Adenylate cyclase plays a vital role in changing neurotransmitters after they have left one neuron, passed through the synapse, and linked up to the receptor on the surface of a second neuron. Adenylate cyclase does this by triggering the synthesis of the "second messenger," cyclic adenosine monophosphate (cyclic AMP). Without sufficient adenylate cyclase activity to stimulate the synthesis of cyclic AMP, the flow of messages in the brain in terms of action potentials and neurotransmitters would be disrupted.

In effect, these two enzymes serve the function of keeping neurochemical messages flowing uninterruptedly in the brain. The first enzyme is involved with neurochemicals that keep messages flowing between the cells, whereas the second enzyme is involved with processes that keep messages moving through the interior of the cell. Alcohol in large quantities can disrupt the functioning of both of these enzymes. Moreover, the activity levels of both enzymes have been shown to be significantly lowered in alcoholics in response to alcohol or appropriate stimulation. With regard to the long-term effects of alcohol use, abnormal functioning of adenylate cyclase has been reported in alcoholics with even as much as four years of sobriety.[19] Because enzymatic activity in the brain is linked to feelings of well-being and other emotional states, it is tempting to speculate about such activity in either the origins of alcoholism or in its maintenance once a person has established a pattern of heavy drinking. One way to find out if these problems with an enzyme like adenylate cyclase precede active alcoholism or are a result of it would be to study the enzyme in children of alcoholic parents before they start to drink or in adult children of alcoholics who have never drunk.

A greater incidence of enzyme abnormalities in alcoholic offspring would suggest that these problems are more than merely an outcome of heavy drinking but may actually be genetic, biologic deficiencies linked to the origins of alcoholism.

### Brain Condensation Products

Still another approach to the biologic or disease basis of alcoholism involves studying certain products thought to be formed in the body when people drink alcohol. Whether we drink alcohol as wine, beer, or liquor, once in the body it is promptly changed to a substance called acetaldehyde, which in turn is changed to acetic acid. Before its transformation, however, acetaldehyde can react with the various neurotransmitters in the brain to form still other products. These new chemicals formed by acetaldehyde reacting with neurotransmitters are called condensation products.

The most important condensation products are salsolinol, tetrahydropapaveroline, and $\beta$-carbolines. The first two of these products are called tetrahydroisoquinolines (THIQs), which are a family of chemicals formed by acetaldehyde reacting with dopamine or another aldehyde in the brain called dopaldehyde. $\beta$-Carbolines, on the other hand, are formed when acetaldehyde reacts with the neurotransmitter serotonin.

When either the THIQs or $\beta$-carbolines are infused into the brains of rats or monkeys, these animals begin to drink large quantities of alcohol. Myers, a leader in the research on these condensation products, has reported that after being treated with THIQs, monkeys have consumed as much as the equivalent for humans of two quarts of 80-proof liquor a day for many days.[20]

What is it about these chemicals that can cause such changes in the drinking of research animals? One of the THIQs, tetrahydropapaveroline, appears to be similar to an alkaloid precursor of morphine. In effect, the theory is that tetrahydropapaveroline produces addictive drinking because it is similar to a narcotic.

Heavy drinking after $\beta$-carboline infusions into the brain is thought to occur in another way. When $\beta$-carbolines are infused into the brains of animals, the animals respond with panic and anxiety. Apparently it is these uncomfortable states of high anxiety that lead to increased drinking.

While the research on THIQs and $\beta$-carbolines is interesting, we cannot conclude that these condensation products cause alcoholism in humans. To be sure, infusing these substances into animals' brains dramatically affects their drinking behavior, but uncertainty exists over whether all of these products are actually formed in the human body when alcohol is consumed. The evidence is mixed. Salsolinol is clearly formed in the brain, and there is strong evidence to support this.[21] On the other hand, only one recent study has found evidence for the formation of tetrahydropapaveroline in the brain.[22] Nobody has yet shown the formation in the brain of a type of $\beta$-carboline produced by a reaction between acetaldehyde and serotonin.[23] In addition, because in theory both alcoholics and nonalcoholics produce THIQs, it is unclear why alcoholism develops in some but not in others.

The THIQ and $\beta$-carboline theories of the origin of alcoholism, like virtually all scientific theories, have important missing pieces of scientific data. Nonetheless, they remain intriguing bodies of research and theory about the origins of alcoholism.

### The New Disease Model: A Biopsychosocial Disease

As we have come to understand, alcoholism is not only a psychosocial and sociocultural problem but a biologic problem as well. Given genetic predispositions and a psychosocial environment that encourages repeated exposure to alcohol, illness predictably results. Appreciating the underpinnings of the disease and the sociocultural contexts in which it gets expressed is clearly necessary if we are to understand alcoholism fully and guide its victims to recovery.

Alcoholism is a multidimensional illness; it is a biopsychosocial disease involving the body, mind, and society. This new disease model of alcoholism is a reminder that if alcoholism is to be understood, it must be seen as a human problem, one that affects all of society and not this or that part in isolation from the rest. The recent research, however, in genetics, neurochemistry, and pharmacology emphasizes the importance of biologic factors in alcoholism. Rather than a problem of will power, character, or morality, alcoholism is an illness with critical biologic dimensions that must be ap-

preciated if its devastating effects on individuals and the societies in which they live are to be stopped.

### REFERENCES


1. Tarter RE: The causes of alcoholism: A biopsychosocial analysis, *In* Gottheil E, Druley K, Skoloda T, et al (Eds): Etiological Aspects of Alcohol and Drug Abuse. Springfield, Ill, Charles C Thomas, 1983, pp 173-201

2. Ewing JA: Alcoholism—Another biopsychosocial disease. Psychosomatics 1980; 21:371-372

3. Wallace J: Predicting the onset of compulsive drinking in alcoholics: A biopsychosocial model of alcoholism. Alcohol 1985; 2:589-595

4. Wallace J: A biopsychosocial model of alcoholism. Social Caseworker: J Contemporary Social Work 1989; 70:325-332

5. McClearn G: Genetic studies in animals. Alcohol Clin Exp Res 1981; 5:447-448

6. Harris AR, Allan AM: Alcohol intoxication: Ion channels and genetics. FASEB J 1989; 3:1689-1695

7. Li TK, Lumeng L, McBride WJ, et al: Rodent lines selected for factors affecting alcohol consumption. Alcohol Alcohol 1987; Suppl 1:91-96

8. George FR, Goldberg SR: Genetic approaches to the analysis of addiction processes. Trends Pharmacol Sci 1989; 10:78-83

9. Schuckit MA: Reactions to alcohol in sons of alcoholics and controls. Alcohol Clin Exp Res 1988; 12:465-470

10. Cloninger CR: Genetic and environmental factors in the development of alcoholism. J Psychiatric Treat Eval 1983; 5:487-496

11. Goodwin DW, Schulsinger F, Hermansen L, et al: Alcohol problems in adoptees raised apart from alcoholic biological parents. Arch Gen Psychiatry 1973; 28:238-243

12. Zhukov VN, Varkov AI, Burov YV: Effect of destruction of the brain serotoninergic system on alcohol intake by rats at early stages or experimental alcoholism. Biogenic Amines 1987; 4:201-204

13. Naranjo CA, Sellers CM, Roach CA, et al: Zimelidine-induced variations in alcohol intake by nondepressed heavy drinkers. Clin Pharmacol Ther 1984; 35:374-381

14. Blum K, Elston SFA, DeLallo L, et al: Ethanol acceptance as a function of genotype amounts of brain [met]-enkephalin. Proc Nat Acad Sci USA 1983; 80:6510-6512

15. Borg S, Kvande H, Sedvall G: Central norepinephrine metabolism during alcohol intoxication in addicts and healthy volunteers. Science 1981; 213:1136-1137

16. Wallace J (Ed): New Disease Model of Alcoholism. Newport, RI, Edgehill Publications, 1989

17. Goldstein PB: Pharmacology of Alcohol. New York, Oxford University Press, 1983

18. Franks NP, Lieb WR: Are the biological effects of ethanol due to primary interactions with lipids or with proteins? Alcohol Alcohol 1987; Suppl 1:139-145

19. Tabakoff B, Hoffman PL, Lee JM, et al: Differences in platelet enzyme activity between alcoholics and nonalcoholics. N Engl J Med 1988; 318:134-139

20. Myers RD: Multiple metabolite theory, alcohol drinking, and the alcogene, *In* Aldehyde Adducts in Alcoholism. New York, Alan R Liss, 1985, pp 201-220

21. Wallace J: The relevance to clinical care of recent research in neurobiology. J Subst Abuse Treat 1988; 5:207-217

22. Cashaw JL, Geraghty CA, McLaughlin BR, et al: Effects of acute ethanol administration on brain levels of tetrahydropapaveroline in L-dopa-treated rats. J Neurosci Res 1987; 18:497-503

23. Matsubara K, Fukushima S, Akane A, et al: Tetrahydro-$\beta$-carbolines in human urine and rat brain—No evidence of formation by alcohol drinking. Alcohol Alcohol 1986; 21:339-345

**Addiction Medicine**
**and the Primary Care Physician**

# Chemical Dependency and Drug Testing in the Workplace

JOHN D. OSTERLOH, MD, *and* CHARLES E. BECKER, MD, *San Francisco*

*Urine testing for drug use in the workplace is now widespread, with the prevalence of positive drug tests in the work force being 0% to 15%. The prevalence of marijuana use is highest, and this can be reliably tested. Though it is prudent to rid the workplace of drug use, there is little scientific study on the relationship of drug use and workplace outcomes, such as productivity and safety. Probable-cause testing and preemployment testing are the most common applications. Random testing has been less accepted owing to its higher costs, unresolved legal issues, and predictably poor test reliability. Legal issues have focused on the right to policy, discrimination, and the lack of due process. The legal cornerstone of a good program is a policy that is planned and agreed on by both labor and management, which serves both as a contract and as a procedure in which expectations and consequences are known.*

*The National Institute on Drug Abuse is certifying laboratories doing employee drug testing. Testing methods when done correctly are less prone to error than in the past, but screening tests can be defeated by adulterants. Although the incidence of false-positive results is low, such tests are less reliable when the prevalence of drug abuse is also low.*

(Osterloh JD, Becker CE: Chemical dependency and drug testing in the workplace, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:506-513)

Alcohol and drug abuse is estimated to cost our nation more than $160 billion per year in lost productivity, health care costs, and crime. We are continually reminded in the news media of the ever-present effects of drug and alcohol abuse. Health care professionals see the effects of drug and alcohol use on the health of our population. The annual cost of therapy for alcohol and drug abuse is $1.6 billion.[1,2] Drug abuse has extended into all levels of society including the workplace. To rid the workplace of drugs, the prevalence of drug abuse needs to be known as well as whether, in fact, such abuse is directly related to workplace outcomes such as productivity, safety, and product integrity. If drug testing is one method of lowering the incidence of drug abuse in the workplace, will it be cost-effective if drug use is less prevalent than we have estimated, and will drug testing be effective in solving this problem either by deterrence or remediation?

Much of what is estimated about the use of drugs in the workplace is from survey or interview data that have been extrapolated to the general population. This is reasonable to do because a sizable proportion of the general population is working. Some of these data, however, are biased toward an overestimation because of their focus on drug abusers within sampled populations. Many surveys have focused on specific populations such as patients attending hospital emergency departments, clinical laboratory results, drug user "hotlines," poison control center phone calls, reports from medical examiners, drug enforcement agency confiscations, and drugs used by intoxicated drivers.[3-6] While such reports tend to emphasize the seriousness of the drug abuse problem, they do not actually estimate the prevalence of drug use in the workplace.

The credibility of alcohol and drug use estimates has recently been called into question.[7-9] Past estimates from the National Institute of Mental Health on the number of persons with alcoholism in the United States were, in part, based on a survey questionnaire that did not include questions about alcoholism per se.[7] Drinking behavior and how it is defined have changed over the years, making comparisons with past estimates less intelligible. Larger surveys by the National Institute on Drug Abuse (NIDA), the National Household Survey on Drug Abuse and the High School Seniors Survey, have inherent errors due to self-reporting. Adolescent survey respondents tend to overestimate actual drug use. Nevertheless, it is alarming to note that 36.3% of high school seniors have used marijuana and 10.3% have used cocaine in their lifetimes. Studies recently done by the National Institute of Mental Health have indicated that in a survey of 20,000 people covering five geographic areas across the United States, 6.8% have alcohol abuse or dependence problems and 2% abuse or are dependent on illicit drugs.[7] These data still do not direct us to the magnitude of the problem of actual drug abuse in the workplace.

Within the medical workplace, 3% of physicians have a history of drug dependence and 10% admit currently using

From the Departments of Laboratory Medicine (Dr Osterloh) and Medicine (Drs Osterloh and Becker), University of California, San Francisco, School of Medicine, and the Toxicology Laboratories (Dr Osterloh) and Divisions of Occupational Medicine and Toxicology (Dr Becker), Northern California Occupational Health Center, San Francisco General Medical Center.

Reprint requests to John Osterloh, MD, Toxicology Laboratory, Rm 3501, San Francisco General Medical Center, 1001 Potrero Ave, San Francisco, CA 94110.

ABBREVIATIONS USED IN TEXT

GC-MS = gas chromatography-mass spectrometry
MRO = medical review officer
NIDA = National Institute on Drug Abuse
PCP = phencyclidine hydrochloride

psychoactive drugs monthly.[10,11] In randomly selected tractor-trailer drivers whose blood and urine were tested for drugs during truck weighing in Tennessee,[12] 15% were positive for cannabinoids, 12% for nonprescription stimulants such as phenylpropanolamine, 5% for amphetamines, and 2% for cocaine. Alcohol was detected in only 1% of the sample. Of recruits for the Chicago Police Department, 20% tested positive for cannabinoids.[13] Actual drug testing data from various laboratories engaged in providing services to industry have indicated that the overall number of positive tests in preemployment testing is around 12% (primarily marijuana), whereas limited random testing data suggest that positive urine tests from currently employed workers is about 2%, primarily due to marijuana. One large testing laboratory has reported the results of testing from seven transportation companies over several years.[14] The rate of drug-positive urine specimens varies from 3% to 16% among these companies. These rates reflect a mixture of test settings including preemployment, random, and probable-cause testing. The data of actual drug use in the workplace are limited. Some have criticized the focus on drugs as misguided because alcohol abuse is a much larger problem and accounts for a larger proportion of morbidity in terms of health effects and accidents.[15]

Even more unclear is the relationship between drug use or abuse and productivity and safety in the workplace. Clearly, workers who are guardians of the well-being of others should not risk the safety of others by using drugs. The general consensus that any chemical may affect judgment or performance is a safe and cautious one. Drugs are often implicated circumstantially in accidents where a cause is not proved. For example, the often-cited air crash aboard the aircraft carrier Nimitz involved drug users. At that time in 1981, it was estimated that 47% (both by survey and direct testing) of sailors used at least one illicit drug, usually marijuana.[16-18] When this disaster occurred, those killed on the flight deck were tested and, not surprisingly, half of these sailors tested positive. In this case, the prevalence of drug use by the sailors on the flight deck merely reflected the prevalence of drug use within the US Navy itself and may not necessarily prove a causal role in this accident. As a corollary, the 65 deaths and 6 accidents aboard US Navy vessels in 1989 seem to have little relationship to the current 3% prevalence of drug-positive urine tests.

The effects of drugs on human performance are not uniform. While alcohol use will clearly alter cognitive and motor function, other drugs are not so well studied. Even in the forensic area of drug-intoxicated drivers who are arrested following accidents or because of the appearance of driving while intoxicated, experts do not agree on which types of human function might be altered by individual drugs.[19] For example, marijuana use may not affect reaction time in terms of stimulus-response reflex, but it can reduce attentiveness.[20-22] Generally the predominant effects of marijuana on behavior and physiology do not last longer than four hours after a marijuana cigarette is smoked, but decrements in performance during complex situations among airline pilots have been measured as long as 24 hours after a dose.[22,23] In conflict with the general assumption that marijuana affects workers' performance are the findings of a study that allowed workers to buy either tobacco cigarettes or marijuana cigarettes. Those using their money to acquire marijuana and smoking as many as 12 marijuana cigarettes each day for the period of the three-week study did not show a difference in work output.[24]

Drug use and abuse is a real problem in society, but the effects of drug use on worker performance and safety need better documentation for us to accurately address these problems. The study of actual illicit drug use, defined dosages, temporal relationships, and effects on work-modeled or real workplace tasks should be addressed with respect to each specific drug in question.

## Goals of Employee Drug Testing

Workplace drug testing may connote both punitive and remedial intent. The anticipated effect of workplace drug testing would be to deter drug use if the consequences of detection are undesirable to the individual user. Detection alone is of little value unless the drug use is discontinued. Most major corporations that have embarked on drug testing have taken remedial action rather than punitive action by providing employee assistance programs. Such programs may reduce costs by providing rehabilitation of an existing employee who "knows the ropes," instead of training a new worker. The overall goals of employee drug testing include improving workplace safety, productivity, and product integrity so that the individual industry will have an improved fiscal bottom line.

Approaches to drug testing have included preemployment, probable cause, safety sensitive, and random testing. Preemployment testing is the most popular type of drug testing program and perhaps the most effective, with the least liability to the employer. Between 60% and 70% of small businesses in one eastern city[25] and 80% of Fortune 500 companies with drug testing programs use the preemployment testing approach.[26] Over a period of years, preemployment drug testing would be expected to lead to a lower incidence of drug use in the work population when drug users are screened out before being hired and old workers leave the work force by natural attrition. Probable-cause testing is useful in enhancing the presumption of drug use when poor performance is observed, evidence of intoxication is witnessed, or after accidents thought to be caused by intoxication. Supervisors and employees can be instructed to recognize the signs of drug intoxication. While the detection of drugs in the urine has no accurate relationship with behavioral or pharmacologic effects, combining witnessed behavior with drug detection can provide a reasonable presumption that drug abuse or drug effects were present.

The random testing of workers by industry is a less popular approach in that it has several shortcomings. To identify most of the drug users in a population using a random testing approach, urine specimens must be collected relatively frequently compared with the period of time that drugs may be present in the urine (Table 1). Random testing should be unannounced so that drug-using workers may not anticipate the time of drug testing and abstain from drug use during that period. This requires an added level of administration and management that may be more costly. While many approaches to drug testing have been examined in the courts

TABLE 1—*Time Intervals for Detecting Drugs in Urine After Use at Cutoff Concentrations*

| *NIDA-Recommended Drug Tests* | *Days Detectable After Use* |
|---|---|
| Marijuana metabolite | |
| Single use | < 7 |
| Ongoing abuse | <30 |
| Cocaine metabolite | < 3 |
| Opiate metabolite | < 2 |
| Phencyclidine | < 7 |
| Amphetamines | < 2 |
| *Others* | |
| Alcohol | < 1 |
| Barbiturates | < 2 |
| Phenobarbital | < 7 |
| Benzodiazepines | < 3 |
| Methaqualone | < 7 |
| Methadone | < 4 |

NIDA = National Institute on Drug Abuse

(safety sensitive, probable cause, and preemployment), the legality of random testing programs has not been decided. Because of the potential for infringing on the right of privacy of individual workers (discussed later) some industries are steering away from random testing (J. Hoerr, K. M. Hafner, G. Degeorge, et al, "Privacy," *Business Week,* March 28, 1988, pp 61-68). While the specificity of drug testing (low false-positive rates) is good when done properly, a low efficiency of such testing may occur when the prevalence of drug abuse is also low. Whenever the prevalence of a test condition (drugs being present) approaches the specificity of a test, the number of false-positive tests relative to the number of true-positives will be high. For instance, phencyclidine hydrochloride is a drug relatively rarely encountered in workplace drug testing programs. If 1 in 1,000 workers actually had phencyclidine in their urine and only 1 in 1,000 false-positive tests occurred in the testing procedure, then half of the positive results in such testing would be false-positive. Clearly, random testing should not be applied to types of drugs with very low prevalence.

This raises the question of which drugs should be tested for. Employers have the choice when working with laboratories to select tests for drugs they think are problematic. Marijuana and cocaine are the drugs most often detected in surveys and programs. Opiates, amphetamines, and phencyclidine are less common. Other drugs, such as barbiturates and benzodiazepines, may also be included in such testing because their use is often encountered among polydrug users. Some drugs in some regions of the country or in certain industries may not be perceived as a problem. If that is the case, employers may wish to spend their money in another area with a higher rate of return.

Recently two studies have shown minimal effects of preemployment drug testing. One study screened all new employees and kept results confidential for a year. Of all the new employees, 12% had tested positive for drug use. There were no differences between drug-positive and drug-negative employees when job performance variables were compared—evaluations and job retention—at the end of the year. Eleven drug-negative employees were fired and no drug-positive employees were fired during the period of this study.[27] In another study, 3,600 workers were hired by the US Postal Service during 1987 and 1988. Overall, 8.4% of all workers hired had positive drug tests (*Clinical Chemistry News,* March 1989, p 8); 13.3% of workers with positive drug tests were fired within six months compared with 9.5% of workers with negative drug tests. While the effects of drug use on work performance have been difficult to document, uncontrolled data from industry have suggested that drug testing in the workplace has been efficacious. Southern Pacific Railroad has indicated that its accident rate has decreased from 10% to 5% over a three-year period of drug testing.[28] General Motors has claimed a greater than 40% reduction in absenteeism, 50% fewer disciplinary actions, and 50% fewer accident claims by employees (J. Castro, J. Beaty, B. Dolan, et al, "Battling the Enemy Within," *Time,* March 17, 1986, pp 52-61). The drug testing program of the military has been exemplary. In the US Navy, the most common drug detected was marijuana. The overall positivity rate has fallen from 48% in 1980 to 3% in 1987.[16,17] While these numbers reflect actual test positivity rates, the numbers from 1980 must be viewed with some skepticism because of the different testing techniques and criteria used in 1980 versus 1983 and thereafter.[17,18]

Because observations in industry have been uncontrolled, critics have argued that drug use may be reduced by deterrence and fear of consequences, but that improvements in safety or productivity may be coincidental. For instance, when accidents occur, attentiveness is subsequently heightened and preventive measures are taken that may reduce accident rates. Also, drug testing has been instituted at a time of labor union weakness and union-busting tactics. Employees may refrain from drug use for fear of losing their jobs in this general milieu. The "Hawthorne effect" can be postulated to be at work because this extra attention to workers and their conditions may improve productivity and morale. Cause and effect have not been documented. Even a corollary hypothesis may be invoked: that poor working conditions with attendant unsafe practices, low worker morale, and low productivity may lead to increased drug use. Overall, drug testing has been viewed as successful in highly regimented situations such as the US Armed Services or in highly focused applications such as preemployment or probable-cause testing.

## Legal Issues

The legal issues that have surfaced in the development of drug testing programs have been reviewed extensively by others.[29-36] Concerns have focused primarily on the right to privacy or lack of probable cause as guaranteed by the 4th Amendment of the Constitution, equal protection with respect to the application of the law by the 14th Amendment, the application of due process and the admissibility of drug test results by the 5th Amendment, and contract law with respect to policy agreements between employers and employees. Also of consideration are government legislation and local law.

While several constitutional and human rights issues have been evolving during the implementation of drug testing in the 1980s, the legal cornerstone of drug testing programs is the emplacement of a policy agreement. Such a policy is a contract between employers and employees. As such, it should be negotiated in advance by both parties and agreed on with respect to the conditions of testing, the procedures for collecting specimens, and the consequences of the test results. Each step in this pathway should be definitively de-

lineated so that choices and contingencies are made by the policy itself and not by others acting after the fact. Employers should guard that policies are evenly applied, are nondiscriminatory, and allow a tested employee adequate recourse to any decision made regarding the employee. Furthermore, each program should include an employee assistance program (see the relevant section). In adopting such policies for drug testing, employers should be aware that local regulations or state legislation may have recently been enacted that affects how such programs would be conducted.

Selecting a group of persons to test without prior suspicion may lead to an allegation of bias or an absence of equal protection. In a ruling against the National Collegiate Athletic Association, the 14th Amendment was cited in part as protection against selecting a group of athletes for drug testing without demonstrating a likelihood that drug use was prevalent in that population. In this particular circumstance, college athletes other than male football and basketball players were found not to have a prevailing drug problem that required testing based on the actual test results in each sport. Due process must be given to a person considered for drug testing. This applies not only to the acquisition of a urine specimen as described by policy procedures, but also with respect to the admissibility of drug testing evidence in court actions. Drug testing techniques must have general scientific acceptance (Frye versus United States)[37] but are not required to have absolute accuracy, only beyond a reasonable doubt (California versus Trombetta).[38]

The most difficult area of constitutional law relates to the 4th Amendment, which prohibits the federal government from unreasonable search and seizure activities. In most cases where there was probable cause, drug testing procedures have been upheld. When applied randomly—that is, without individualized suspicion—the courts have had difficult decisions before them. Some legal opinion has extended the prohibiting of unreasonable search and seizure to an intrusion into individual private lives for both government and private sectors. Other interpreters of the Constitution have suggested that the framers of the Constitution did not intend to protect the private act of illicit drug use but were concerned with the privacy of family life, public service, and economic practices. Executive Order 12564 by then-President Ronald Reagan in 1986 has been applied slowly, primarily to the random testing of employees in safety-sensitive positions, wherein the public concern for safety (such as with airline pilots) or the corruption of a process (customs agents) has been held as exceeding the rights to privacy of the individual. For example, in prison guards who were searched and tested for drugs, a lower court ruled that probable cause should be required before testing. A higher court reversed this decision, indicating that a lack of drug use was necessary for the job function being performed.[39] Drug testing of employees in certain critical positions has been favored as being a type of "fitness test."

Several cases have been decided in favor of the plaintiff because of the invasion of privacy and protection under constitutional law (Luck versus Southern Pacific Transportation Company, Price versus Pacific Refining Company).[40,41] Rulings in favor of the plaintiffs in these cases were contingent on the lack of probable cause and the poor implementation and practice of a policy agreement. A higher court ruling may still be heard in these cases. Also, there are examples of several local jurisdictions that, without adequate policy agreements, have tried to coerce employees into providing urine specimens for drug testing. Such actions, no matter how likely the actual drug problem, were doomed to fail.

## Testing Procedures

For years, many laboratories have been capable of measuring drugs and their metabolites in biologic fluids. These measurements have been used in a number of different circumstances, including clinical emergency toxicology (drug overdose cases), medical examiners' investigations (cause of death determination), methadone testing programs, and therapeutic drug monitoring practices. Until recently, the many different techniques and approaches to detecting drug use have been unique or suited to those particular situations, but widely varied between them. With the development of the National Institute on Drug Abuse guidelines for federal employee drug testing programs in 1988,[42] there has been consensus regarding the types of methods to be used in such testing.[43,44] The following conditions cause employee drug testing to be different from other forms of drug testing:

- The concentrations of drugs are usually lower than in emergency toxicology cases, coroners' cases, or tolerant methadone patients.
- The prevalence of drug use in the populations being tested is often much lower in employee drug testing programs than in selected populations of drug users (methadone testing) or cases where a particular drug is highly likely to be present (clinical signs and history of drug overdose).
- The assurity or reliability of the test result in employee drug testing should be greater than in other forms of drug testing because the drug test results may provide the only evidence that a drug was in fact present. In other clinical testing circumstances, the past history or clinical signs may provide additional evidence and a higher probability that a drug may be present (therapeutic drug monitoring, emergency toxicology). Also, the action or consequence of the drug testing may be more severe for those who have been falsely accused. Thus, the methods for drug testing in the workplace must be both highly sensitive and specific.
- The search for drugs in employees is a focused or a narrow one (usually five illicit drugs or classes) as opposed to a broad search for any drug that might be causing clinical symptoms as in a case of overdose in a hospital emergency department.

Testing for marijuana and cocaine, the two most commonly abused drugs, appears to be the most productive, but the advocates of drug testing programs have been criticized for not including the most common of all abused drugs—alcohol. As stated earlier, programs that focus on drugs abused in very low prevalence may also be misguided because false-positive results may outnumber true-positive results when the prevalence approaches the specificity of the testing.

The NIDA has prescribed that the initial screening test be an immunoassay (radioimmunoassay, enzyme immunoassay, fluorescent polarization immunoassay) for the five major illicit drugs of abuse: marijuana, cocaine, amphetamines, phencyclidine (PCP), and opiates.[42] Positive results by the initial screening methods would then be confirmed subsequently by gas chromatography-mass spectrometry (GC-MS). The cutoff (detection of the presence of the drug) concentrations of these methods are listed in Table 2.

No method has absolute accuracy, and any can be fooled by similar drugs or intentional adulteration. Drug testing results may be inaccurate because of analytic false-positive or -negative findings or owing to the misapplication of the results. Usually, drugs or chemicals that produce false-positive or -negative results in the screening assay will not produce the same problem in the confirmatory assay. Agents initially causing a false-negative test, however, might not produce further confirmatory testing. Therefore, the aim of drug users wishing to avoid detection has been to interfere with the initial immunoassay screening test. Fluorescent polarization immunoassays for barbiturates and benzodiazepines can be rendered falsely positive by the use of nonsteroidal anti-inflammatory agents such as ibuprofen.[45] Also, the presence of fluorescein dye in the urine may prevent determination by fluorescent polarization immunoassays.[46,47] Gas chromatographic-mass spectrometric procedures can also be fooled. It has recently been shown that ibuprofen will cause a false-negative result in some GC-MS confirmatory tests for marijuana metabolites. This is probably due to the consumption of the derivatizing agent by ibuprofen, which is necessary to make marijuana volatile for gas chromatographic analysis.[48] Other immunoassays, such as enzyme immunoassays, have been shown to produce false-negative results by additives such as benzalkonium chloride (an antiseptic used topically and as an antimicrobial preservative in ophthalmic solutions such as Visine eye drops), vinegar, lemon juice, goldenseal *(Hydrastis canadensis)* tea, lye crystals for unplugging drain pipes, and liquid soap. All but the benzalkonium chloride are required in high concentrations and are easily detected by simple means such as determining the pH, specific gravity, shake tests for foaming, creatinine concentrations, and osmometry. The use of benzalkonium chloride from Visine eye drops has been shown to cause false-negative results in enzyme immunoassays for marijuana and cocaine and can only be ruled out by testing specifically for benzalkonium chloride.[49-52] A recidivistic drug user may use other approaches such as diluting the urine specimen with toilet water, substituting for the urine specimen a known drug-free urine specimen, ingesting substances that dilute the urinary concentration of the drug to be detected (drinking water, taking diuretics), ingesting acidic salts such as ammonium chloride to hasten the excretion of basic drugs before the urine collection or ingesting basic salts (sodium bicarbonate) to reduce the excretion of basic drugs during collection.

Apart from these purposely added or ingested adulterants that may cause false results, a potential problem is the misidentification of drugs taken innocently without pharmacologic effects or therapeutically. Usually the confirmatory testing procedures can rectify the misidentification caused by a cross-reactivity of the immunoassays with similarly structured drugs. Drugs that cross-react with the initial screening immunoassay test are listed in Table 3. For the opiates, medications with codeine, hydrocodone bitartrate (cough syrups), and oxycodone hydrochloride will cause the initial immunoassay to be positive for opiates. Subsequent GC-MS will differentiate these drugs from morphine. Similarly, over-the-counter stimulants such as dietary aids and decongestants (phenylpropanolamine, fenfluramine, and ephedrine) may cause the initial immunoassay screen for amphetamines to be positive. Again, GC-MS differentiates these from illicit amphetamines. Consuming poppy-seed-containing foods (bagels, poppy-seed cakes) will produce detectable amounts of morphine in the urine without sufficient amounts reaching the systemic circulation to produce any pharmacologic effects. Usually the morphine derived from the use of heroin (diacetyl morphine) must be metabolized to monoacetyl morphine and morphine. Therefore, to differentiate poppy-seed use from heroin abuse, the presence of monoacetyl morphine in a GC-MS analysis will implicate heroin use.[53,54]

Actual false-positive tests are rare when these two testing procedures are combined. The only standardized way of assessing the accuracy of employee drug testing is by providing proficiency test specimens for laboratories to test in an open or a blind manner. Recent studies on employee drug testing have shown that laboratories using these methods are highly accurate, having very low false-positive rates when focused on only the five drug classes.[55,56] A number of writers have concentrated on proficiency testing results that are not applicable to employee drug testing. Unfortunately, these results have also received media attention. Most of the previously published reports on proficiency testing results have surveyed laboratories doing work for methadone drug testing centers and hospital emergency toxicology services. As indicated, the concentrations of drugs, the number and types of drugs, the prevalence of drugs in the population tested, and the techniques used in these different situations are not comparable.

Calibration and in-house quality-control checks are routine in any laboratory. In addition, the NIDA guidelines for

TABLE 2—*NIDA-Recommended Cutoff Concentrations in Urine (ng/ml) for Workplace Drug Testing*

| *Drug* | *Immunoassay Screen, ng/ml* | *GC-MS Confirmation, ng/ml* |
|---|---|---|
| Marijuana metabolite* | 100 | 15 |
| Cocaine metabolite† | 300 | 150 |
| Opiate metabolite | 300‡ | 300§ |
| Phencyclidine | 25 | 25 |
| Amphetamine | 1,000‖ | 500¶ |

GC-MS = gas chromatography-mass spectrometry, NIDA = National Institute on Drug Abuse

*Δ-9-Tetrahydrocannabinol-9-carboxylic acid.
†Benzoylecgonine.
‡Total conjugated opiates; 25 ng/ml if by radioimmunoassay for free morphine.
§Either codeine or morphine after hydrolysis.
‖Total reacting amphetamines.
¶Either D-amphetamine or methamphetamine.

TABLE 3—*Common Cross-reacting Drugs in Screening Immunoassays*

| | |
|---|---|
| *Amphetamines** | *Opiates* |
| Phenylpropanolamine | Oxycodone |
| Pseudoephedrine | Hydrocodone |
| Ephedrine | Hydromorphone |
| Phenylephrine | Codeine |
| Phentermine | *Marijuana metabolite* |
| Propylhexedrine | NSAIDs before 1986 |
| L-Methamphetamine† | Naltrexone, nabilone do *not* cross-react |
| Fenfluramine | *Cocaine metabolite* |
| Other amines | Local anesthetics and atropine do *not* cross-react |

NSAIDs = nonsteroidal anti-inflammatory drugs

*Several manufacturers (SYVA, Abbott) now make a more specific immunoassay for amphetamines that cross-react less with other amines.
†In Vicks Inhaler (as desoxyephedrine).

contractors with federal agencies require that 50% of all specimens submitted by the agency in the first quarter should be blind quality-control specimens. About 80% of these urine specimens should not contain drugs. In subsequent quarters, 10% of the specimen load is to be for the purposes of blind quality control. It is required that the cost of preparing and testing these specimens is to be borne by the submitting agency. Also, ten proficiency testing specimens are sent every two months to the laboratories certified by the NIDA program. Any false-positive test requires consideration for recertification of the laboratory and a reanalysis of previous contract specimens. To date, of the initial 100 laboratories that applied, only about 40 have been certified by NIDA. More than 60 had dropped out because of the stringent requirements (including a one-week inspection and operations observation). Others have had difficulty because of the added requirement of quantitation (determine concentration) during the GC-MS confirmatory procedures.

The reliability of any test depends on the previous probability of the test condition being present and the analytic sensitivity and specificity of the test. If the tests for marijuana and PCP are both 99.9% specific (0.1% false-positives) and these two tests are applied to a population of 1,000 persons where only 1 person has PCP in their urine and 100 have marijuana metabolite in their urine, the reliability (predictive value, posterior probability) of a positive test for marijuana in this situation is 99% and for PCP is only 50%. While both tests have the same analytic specificity, the relative number of false-positive to true-positive tests will be much higher in the low-prevalence situations—that is, PCP use.

In addition to testing urine to detect drug use, hair analysis for drugs has been investigated. Many drugs have been detected in hair, but the interpretations of these tests are at present vague. Although hair specimens can be obtained repeatedly and noninvasively, can be identified as belonging to particular persons, and are less likely to be adulterated, drugs present in hair cannot substantiate current use. Therefore, hair analysis is unlikely to be used in probable-cause testing. Also, hair as a specimen suffers potentially from external passive contamination. Hair analysis was reviewed recently by Baumgartner and co-workers.[57]

## Testing Programs

Before establishing a drug testing program and developing the necessary policy to make such a program work, the need for such a program should be established and documented. If a drug abuse problem has been shown to be present in a particular workplace, it is more likely that all those concerned—employers, employees, unions, regulatory agencies, and legislative or legal bodies—will be able to join forces in efforts to help solve the drug problem. In the absence of a clear need for a drug testing program, accusations of bias or discrimination may be charged more easily. Documenting a drug abuse problem may take several forms, including the witnessed behavior of intoxication or drug dealing on the job, increased accidents in an environment of suspected drug use, or anonymous pilot testing of employees to document the presence of drugs. In one workplace where almost 500 preemployment tests were done, only one PCP-positive employee was found at a cost of more than $16,000 for the testing alone.[58] This might not be considered cost-effective, but if that person were to cause a costly accident or error, these dollars may have been well spent.

The development of a policy for drug testing should include the following:

- A statement of the need for drug testing and why drug use is unacceptable;
- Policy development should be an ongoing process that involves comment and consideration from the employees. It is also in the employees' interest to have a safe, productive, and profitable workplace;
- The procedure for collecting urine specimens should be clearly and definitively stated so that employees know exactly what is expected;
- All procedures should be standardized to ensure a fair application to all employees. These procedures should be carried out on a mock basis to ensure they are actually workable before the first employees are entered into the process;
- The consequences of detection should be clearly stated for each alternative;
- Alternatives must include remediation and rehabilitation.[35,42,59]

Following agreement among the participating parties, the actual procedure should be defined. If random testing is to be done, choosing the appropriate time for collection may present some difficulty. If employees are aware or notified that collections will occur, the purpose of the program may be defeated. If random collections are not frequent enough, testing would tend to identify only continuous abuse. Random collections may be made at times when other activities are scheduled within the operations of an industry. For example, collections may be done during routine medical examinations (annual physicals), during corporate health surveys, during operations shutdowns for preventive maintenance or safety inspections, and during insurance enrollment periods. Other random collection techniques include the checking of random portions of the worker population. For instance, using random number generation, only 10% of the work force would be sampled.

Other specimen collection schemes relate to the program, whether probable cause, safety sensitive, or preemployment. Probable-cause testing is the most common program for testing currently employed workers. The written documentation of witnessed behavior that corroborates test results is extremely important in such a program. Employers should be instructed as to what signs to observe in a worker who is suspected of intoxication. Because probable-cause testing only tests persons who have been presumed to use drugs because of their behavior or symptoms, only the worst offenders are likely to be identified. It is usually preferable that a worker's supervisor document his or her observations and accompany the person who is under suspicion of drug use to where a urine specimen would be collected.

The urine specimen should be collected in an area away from use by other employees so that the occurrence of testing does not become public knowledge. The direct observation of urination is not absolutely necessary, but some precautions should be taken. The subject to be tested should not be allowed to carry extra garments, purses, or packages into the toilet area. The toilet area should be free from other cups, containers, or water faucets. The toilet water should be dyed with a commercial sanitary indicator. Although drug users in methadone programs or the criminally incarcerated have sophisticated techniques to adulterate urine or escape detection, such sophistication is not commonplace in the work

force. Therefore, direct observation is considered more of an invasion of privacy than a necessary or valid procedure. Once the urine specimen is collected, the temperature should immediately be measured and recorded; it should be within 2°C of the body temperature. The urine specimen should then be closed and sealed. The employee and the person who is witnessing the collection process should initial and date the seal or the label of the container and sign a log book that is kept on the premises. Special tamper-proof containers with seals that will tear irreparably when opened can be purchased for such drug testing. Specimens to be transported to laboratories for testing should be packaged in tamper-proof courier bags or locked boxes with the keys or combinations known only by the laboratory. Attached either to an individual specimen or the box of specimens should be a list of the persons who have handled the specimens, and their signature should record their contact with the specimens.[42,59]

The laboratory should report only confirmed positive results; all other test results are to be reported as negative. Reporting results such as "trace," "positive but unconfirmed," or "unknown substances present" should be strongly discouraged. Policy should provide for the retesting of a specimen at a laboratory of the employee's choice. Medical review officers (MRO) are considered an important component of drug testing programs and are mandated for federal programs.[42] Their duties include the understanding of how tests were done, how specimens were acquired, how to interpret the results, and what courses of action can be taken. A designated MRO also serves as a person outside the corporate structure who can confidentially review with the employee the results of testing and the circumstances leading to positive test results. In so doing, the MRO must understand what are the cutoff concentrations for individual drugs and the period of time during which individual drugs can be detected. The MRO must also understand which drugs and conditions may alter the results of drug testing. Most important, the MRO must be able to communicate the meaning of test results to administrative personnel who may take action against the individual employee. Drug test results *do not* indicate the following: They do not reveal the extent of use. A positive drug test result may indicate either solitary one-time use or continual abuse of a particular drug. Urinary drug testing does not correspond to either pharmacologic effects or effects on workplace performance. Drug test results only record that the drug was present in the urine. Drug test results do not indicate when the drug was taken or how much was taken.

The courses of action available to an MRO should be guided explicitly by policy. The alternatives that the MRO may choose from include no action, explanation by the employee of conditions leading to the positive test, an investigation of medications that may have been prescribed, repeating the test with a full explanation of consequences when a second specimen is positive, a change of position within the company, a leave of absence, further performance evaluation, resignation, and termination. With all of the above alternatives, counseling and treatment should be provided through a practitioner with experience in drug abuse and rehabilitation.

## Employee Assistance Programs

Chemical dependency in the workplace may present as acute intoxication, chronic abuse, withdrawal, or as accelerated medical complications of chemical dependency such as liver disease. Intoxication, withdrawal, and medical complications of chemical dependency are more obvious but occur less frequently than the more subtle, less specific signs of drug use such as absenteeism, tardiness, or accidents.

The key to intervening and treating a drug user is early identification and the institution of care.[60,61] As an outgrowth of occupational alcoholism programs, most Fortune 500 companies now have some form of employee assistance program. Employers can encourage employees to use such programs. Because of the tendency for a troubled employee to deny the extent of his or her addiction, intervention techniques have been developed for the purpose of directing identified persons into a structured program. Denial may go beyond the affected person to involve co-workers, supervisors, and family. An effective intervention makes clear to a chemically dependent worker that both health and economic livelihood are at stake. The clinicians conducting the intervention may use family members and co-workers familiar with the troubled employee's deteriorating physical and emotional states.

After an appropriate clinical evaluation is made by either a member of the company's employee assistance program or a consulting clinician, the next step is directing the substance-abusing person into treatment.[62] In some case evaluations, what is perceived as behavioral problems associated with possible drug use may be the clinical manifestations of a primary emotional disorder such as depression. If chemical dependency is diagnosed, the employee might be referred to a 28-day inpatient drug treatment program. If a primary emotional disorder is diagnosed, a referral may be made for outpatient psychotherapy. Treating an emotional disorder will not be effective unless chemical dependency is also treated, and the 28-day inpatient treatment programs have become the standard for treating chemical dependency. The cost of such programs is high, and for some employees with less-than-optimal health insurance coverage, a more circumscribed period of inpatient care can be followed by care in a halfway house or residential treatment setting.

Several models exist for the treatment of chemical dependency.[63] The need for self-participation is stressed by Alcoholics Anonymous and Narcotics Anonymous. For a recovering alcoholic or drug addict, this self-help group approach is often crucial in maintaining a state of sobriety. Most treatment programs use some form of group psychotherapy in addition to the "12-Step" approach of Alcoholics Anonymous. It is often only through the group context that a chemically dependent worker can come to terms with his or her long-term avoidance of the acknowledgement of the addictive process and its negative effects on the person's life. Other psychotherapeutic modalities may include individual and family therapy.

Chemically dependent workers usually require a defined structure, guidelines, and rules. The inpatient treatment model is often the best means for initially creating such a framework. A medical history and physical examination with appropriate laboratory testing are necessary on entering treatment. The greatest chance of success with a chemically dependent worker occurs when the program emphasizes total abstinence, but even with such measures "slips" do occur. Chemically dependent adults must consider themselves "in the process of recovering" on an indefinite basis. Persons with alcoholism may require pharmacologic support with

disulfiram to decrease their recidivism. A medical evaluation may indicate the need for an antidepressant medication or lithium carbonate for treating an associated affective disorder.

Occupational physicians should contribute to the design of employee assistance programs.[62] Such a program may be situated within a company or outside the company as a contracting service. All employee assistance programs should provide evaluation, treatment referral, follow-up, and employee education. Other services include short-term treatment, management training, drug monitoring, and organizational consultation to departments in the company. A properly run program maintains confidentiality in self-referral cases and makes clear the limited confidentiality in a management referral. Other planning functions of the medical consultant include a review of health insurance benefits for the treatment of substance abuse and psychiatric illness. Part of the cost-effectiveness of employee assistance programs is the educational effort directed at management and employees around the hazards of substance abuse. Managers can be instructed about the early warning signs of drug abuse. Employees can learn of the acute and long-term effects of alcohol and other substance use. The ultimate goal in such educational efforts is to encourage chemically dependent workers to seek assistance for their addictive disease.

As difficult as these problems are to treat, great satisfaction can be had in helping a dysfunctional, chemically dependent worker to return to a premorbid level of occupational and personal functioning. The professional challenge is great in overcoming the resistance to treatment on the part of the employee and the negative feelings engendered on the part of the health practitioner. While there is a need for flexibility in approaching any troubled person, companies and their consulting health care team should also have a set of policies and procedures for addressing the problems of chemically dependent and emotionally disturbed employees.

## REFERENCES


1. Hawks RL, Chiang CN (Eds): Urine Testing for Drugs of Abuse, US Dept of Health and Human Services publication No. (ADM) 87-1481. Natl Inst Drug Abuse Res Monogr Ser [73] 1986
2. Nation's expenditures for alcohol, other drugs, in terms of therapy, prevention, now exceed $1.6 billion. JAMA 1987; 258:20-23
3. Bailey DN: Comprehensive toxicology screening: The frequency of finding other drugs in addition to ethanol. Clin Toxicol 1984; 22:463-471
4. Litovitz TL, Schmitz BF, Holm KC: Annual report of American Association of Poison Control Centers National Data Collection System. Am J Emerg Med 1988; 7:495-545
5. Caplan YH, Ottinger WE, Park J, et al: Drug and chemical related deaths: Incidence in the state of Maryland—1975 to 1980. J Forensic Sci 1985; 30:1012-1021
6. Frank RS: Drugs of abuse: Data collection systems of DEA and recent trends. J Anal Toxicol 1987; 11:237-241
7. Barnes DM: Drugs: Running the numbers (News). Science 1988; 240:1729-1731
8. Schuster CR: The United States' drug abuse scene: An overview. Clin Chem 1987; 33(suppl):7B-12B
9. Kozel NJ, Adams EH: Epidemiology of drug abuse: An overview. Science 1986; 234:970-974
10. McAuliffe WE, Rohman M, Santangelo S, et al: Psychoactive drug use among practicing physicians and medical students. N Engl J Med 1986; 315:805-810
11. McAuliffe WE, Wechsler H, Rohman M, et al: Psychoactive drug use by young and future physicians. J Health Soc Behav 1984; 25:34-54
12. Lund AK, Preusser DF, Blomberg RD, et al: Drug use by tractor-trailer drivers. J Forensic Sci 1988; 33:648-661
13. Ostrov E, Cavanaugh JL: Validation of police officer recruit candidates: Self-reported drug use. J Forensic Sci 1987; 32:496-502
14. Whitney J: Drug use patterns found in criminal justice and workplace drug testing programs. Calif Assoc Toxicol Newslett Fall 1989, pp 21-28
15. McBay AJ, Hudson P: Cost-effective drug testing. J Forensic Sci 1987; 32:575-579
16. Urinalysis Test Results Analysis, December 8, 1980. Arlington, Va, Booz Allen & Hamilton, Inc, 1981
17. Needleman SB, Romberg RW: Comparison of drug abuse in different military populations. J Forensic Sci 1989; 34:848-857
18. Hilderbrand RL: The US Navy Drug Testing Program. Calif Assoc Toxicol Newslett Winter 1986, pp 22-24
19. Consensus Development Panel: Drug concentrations and driving impairment. JAMA 1985; 254:2618-2621
20. McBay AJ: Interpretation of blood in urine cannabinoid concentrations. J Forensic Sci 1988; 33:875-883
21. Mason AP, McBay AJ: Cannabis: Pharmacology and interpretation of effects. J Forensic Sci 1985; 30:615-631
22. Jones RT: Drug of abuse profile: Cannabis. Clin Chem 1987; 33(suppl): 72B-81B
23. Yesavage JA, Leirer BO, Denari M, et al: Carry-over effects of marijuana intoxication in aircraft pilot performance: A preliminary report. Am J Psychiatry 1985; 142:1325-1329
24. Mello NK, Mendelson JH: Operant acquisition of marijuana by women. J Pharmacol Exp Ther 1985; 235:162-171
25. Godefroi R, McCunney RJ: Drug screening practices in small businesses—A survey (Letter). J Occup Med 1988; 30:300, 302
26. Drug Testing in Major US Corporations: A Survey of the Fortune 500. Raleigh, NC, Noel Dunivant and Associates, 1985
27. Parish DC: Relation of the pre-employment drug testing result to employment status: A one year follow-up. J Gen Intern Med 1988; 4:44-47
28. Taggart RW: Southern Pacific: A success story—Forensic Drug Testing Newsletter. Washington, DC, American Assoc of Clinical Chemistry, December 1989
29. Council on Scientific Affairs: Issues in employee drug testing. JAMA 1987; 258:2089-2096
30. Chamberlain RT: Legal issues related to drug testing in the clinical laboratory. Clin Chem 1988; 34:633-636
31. Adams WF, Remmers CL: Drugs and alcohol in the workplace: Technology, law and policy. Santa Clara Comput High-Technol Law J 1986; 2:305-388
32. Imwinkelried EJ: Some preliminary thoughts on the wisdom of governmental prohibition or regulation of private employee urinalysis testing. Clin Chem 1987; 33(suppl):19B-32B
33. Chamberlain RT: Legal considerations in drug use testing: Privacy rights, contracts and wrongful use of test results. J Forensic Sci 1989; 34:1477-1481
34. Long KL: The discovery process in drug use testing litigation. J Forensic Sci 1989; 34:1454-1470
35. Substance-Abuse Testing Committee: Clinical issues in urinalysis of abuse substances. Clin Chem 1988; 34:605-632
36. Angarola RT: Drug detection programs in industry. Pharm Chem Newslett 1984; 13:1-11
37. Frye v United States, 293 F 1013 (DC Cir 1923)
38. California v Trombetta, 467 US 479, 104 SCt 2528, 81 L Ed2d 413, 1984
39. McDonnell v Hunter, 809 F2d 1302 (8th Cir) 1987
40. Luck v Southern Pacific Transportation Co, 843230 SF Super Ct, Calif
41. Price v Pacific Refining Co, 29200 (Contra Costa, Cal Super Ct, Feb 10,1987)
42. Mandatory Guidelines for Federal Workplace Drug Testing Programs; Final Guidelines; Notice. Federal Register 1988 Apr 11; 53(69):11970-11990
43. Hoyt DW, Finnigan RE, Nee T, et al: Drug testing in the workplace—Are methods legally defensible? A survey of experts, arbitrators and testing laboratories. JAMA 1987; 258:504-509
44. Counsel on Scientific Affairs: Scientific issues in drug testing. JAMA 1987; 257:3110-3114
45. Larsen J, Fogerson R: Nonsteroidal anti-inflammatory drug interference in TDx assays for abused drugs. Clin Chem 1988; 34:987-988
46. Inloes R, Clark D, Drobnies A: Interference of fluorescein, used in retinol angiography, with certain clinical laboratory tests. Clin Chem 1987; 33:2126-2127
47. Elin RJ, Bloom JN, Herman DC, et al: Interference by intravenous fluorescein with laboratory tests. Clin Chem 1989; 35:1159-1160
48. Brunk SD: False negative GC-MS assay for carboxy THC due to ibuprofen interference. J Anal Toxicol 1988; 12:290-291
49. Warner A: Interference of common household chemicals in immunoassay methods for drugs of abuse. Clin Chem 1989; 35:648-651
50. Pearson SD, Ash KO, Urry FM: Mechanism of false-negative urine cannabinoid immunoassay screens by Visine eye drops. Clin Chem 1989; 35:636-638
51. Mikkelsen SL, Ash KO: Adulterants causing false-negatives in illicit drug testing. Clin Chem 1988; 34:2333-2336
52. Hurrell Y, Spiehler V: Adulterants intended to cause false negatives in urine screens for marijuana or cocaine use. Clin Chem 1989; 35:1175
53. Mule SJ, Casella GA: Rendering the 'poppy-seed defense' defenseless: Identification of 6-monoacetylmorphine in urine by gas chromatography-mass spectroscopy. Clin Chem 1988; 34:1427-1430
54. ElSohly HN, Stanford DF, Jones AB, et al: Gas chromatographic/mass spectrometric analysis of morphine and codeine in human urine of poppyseed eaters. J Forensic Sci 1988; 33:347-356
55. Davis KH, Hawks RL, Blanke RV: Assessment of laboratory quality in urine drug testing—A proficiency testing pilot study. JAMA 1988; 260:1749-1754
56. Frings CS, Battaglia DJ, White RM: Status of drugs-of-abuse testing in urine under blind conditions: An AACC study. Clin Chem 1989; 35:891-894
57. Baumgartner WA, Hill VA, Blahd WH: Hair analysis for drugs of abuse. J Forensic Sci 1989; 34:1433-1453
58. Bompey SH: Drugs in the workplace: From the batter's box to the boardroom. J Occup Med 1986; 28:825-832
59. Consensus Summary of Interdisciplinary Approaches to the Problem of Drug Abuse in the Workplace. Washington, DC, National Institute on Drug Abuse, US Dept of Health and Human Services publication No. (ADM) 86-1477, 1986
60. Austin RL: Employee assistance programs. Clin Chem 1987; 33(suppl):101B-105B
61. Peterson KW, Austin RL, Garvin FH, et al: Panel discussion: Counseling, treatment, and employer response. Clin Chem 1987; 33(suppl):106B-112B
62. Walsh DC, Hingson RW: Where to refer employees for treatment of drinking problems. J Occup Med 1985; 21:745-752
63. Garvin FH: Laboratory assessments in treatments of substance abuse: Utilization and effects on treatment design. Clin Chem 1987; 33(suppl):95B-100B

# The Role of Physicians as Medical Review Officers in Workplace Drug Testing Programs

## In Pursuit of the Last Nanogram

H. WESTLEY CLARK, MD, JD, MPH, *San Francisco*

*In discussing the role of physicians in workplace drug testing programs, I focus on the recent Department of Transportation regulations that require drug testing in such regulated industries as interstate trucking, air transportation, mass transit, and the railroads. These regulations require that applicable drug testing programs employ physicians as medical review officers to evaluate positive tests that have been screened and confirmed by different techniques to determine if there is a legal medical explanation for the result. The drug testing program tests for the presence of amphetamine, cocaine, tetrahydrocannabinol, opiates, and phencyclidine. If an employee testing positive has an acceptable medical explanation, the result is to be reported as negative. Little practical advice exists for medical review officers, and they must be aware of key elements of the regulations and potential trouble spots.*

(Clark HW: The role of physicians as medical review officers in workplace drug testing programs—In pursuit of the last nanogram, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:514-524)

In the past four years, there has been increased pressure for employers to test their employees for drug use in the workplace.[1] This pressure has come from employers themselves.[2,3] Many have come to believe that despite the lack of accurate data documenting the magnitude of illness, disability, and monetary consequences of drug abuse in the workplace, the possible risks are enough to warrant drug testing.[4] Substantial pressure has also come from the federal government.[5] Finally, the public has expressed its support for urine testing of employees, especially those in safety-sensitive positions. Some believe, however, that our nation's preoccupation with the "war on drugs" is being used to tolerate unreasonable encroachments on basic constitutional rights to privacy and against unreasonable search and seizure.[6] Others argue that the ethical basis for drug testing is unsound.[7]

The apparent controversy about drug testing in the workplace stems more from the use of preemployment, scheduled, and random drug testing than from for-cause testing. Obviously, for-cause testing is directed at persons who are either involved in workplace accidents or who behave in a "suspicious" way. On the other hand, preemployment, scheduled, and random urine testing are directed more at preventing and deterring drug abuse.[8,9] Routine testing screens blindly, casting a net among the users of illicit drugs and nonusers alike. As a result, those who are not so concerned about the ethical and legal issues usually become concerned about the process of drug testing, wanting reassurances that they will not become unwitting victims of the war on drugs.

A major concern of many is the question of whether laboratories know what they are doing.[10,11] To pursue both a national policy against psychoactive drug use in America and an industrial policy of no such drug use in the workplace, it has become necessary to recognize that drug testing must be treated as a forensic process, complete with documentation, chain of custody, quality control, and the proper interpretation of results.[12] Indeed, professionals involved with laboratories and clinical toxicology have debated the prerequisites for adequate drug testing processes and procedures in the academic and clinical literature. The objective of this debate was to ensure, where possible, that no person be falsely accused of using illicit drugs as a result of inadequate or poorly conducted drug tests.[13] Thus, a substantial number of papers have addressed the issues that inhere in the collection of urine and its subsequent testing.[4,11,12,14-17]

A second major concern is privacy. While there are a number of components to the issue of privacy, one basic issue often unstated by proponents of urine testing is the direct observation of urination. Some experts do not hesitate to recommend the direct observation of urination for the purpose of producing a specimen for drug testing.[8,18] In situations like the military where individual rights are understood to be subservient to a larger mission, direct observation can be done with impunity.[9] For many people, however, bodily functions are private functions; the thought of strangers observing these functions, even in pursuit of a higher ideal such as a drug-free workplace, is unthinkable and unacceptable.[6] This view is even more understandable when the majority of workers are not using illicit drugs.

Policymakers have turned for advice to the drug testing industry and to experts who have clinical familiarity with the urine collection and testing process. Many who have experience with the drug testing process acquired their experience from such programs as methadone maintenance or other drug treatment programs; in these situations, the clinicians are often involved in a cat-and-mouse game with career sub-

From the Department of Psychiatry, University of California, San Francisco, School of Medicine, and the Substance Abuse Inpatient Unit, Department of Veterans Affairs, Veterans Administration Medical Center, San Francisco.

Reprint requests to H. Westley Clark, MD, JD, MPH, Department of Veterans Affairs, VA Medical Center, 4150 Clement St, San Francisco, CA 94121.

ABBREVIATIONS USED IN TEXT

DOT = US Department of Transportation
GC-MS = gas chromatography-mass spectrometry
MRO = medical review officer
NIDA = National Institute on Drug Abuse
THC = tetrahydrocannabinol

stance abusers who themselves have developed skills to match those of their clinicians. Thus, those who are testing are often matching wits with those who are being tested. For example, several researchers have investigated additives claimed by addicts to produce false-negative tests and found some merit to these claims; such common substances as table salt, household vinegar, liquid bleach, concentrated lemon juice, liquid hand soap, tetrahydrozoline hydrochloride (Visine) eye drops, and goldenseal *(Hydrastis canadensis)* tea have been used by addicts to alter their urine specimens.[18-20]

In this vein, at least one laboratory specialist was reported to say that people would find creative ways to get around urine screening and that the technology of evading drug tests will parallel the technology of detection.[21] Indeed, there are publications available for the public informing them about urine tests ("The Dope on Urine Tests," *San Francisco Bay Guardian,* 1990; 24:8, contained a brief "alert" informing readers that they could get a booklet that would help them pass urine tests. The booklet, "Conquering the Urine Drug Tests," can be purchased from Byrd Laboratories, 225 Congress #40, Austin, TX 70701). Because it is not clear how many casual users of drugs have developed the sophistication at deception found in career drug users, it can safely be said that a policy that encourages deception and evasion among casual drug users, rather than deterrence and prevention, is undesirable.

Drug testing experts are more likely to recommend the strict processes that appear to work for career drug users.[8] Consequently, such recommended precautions as random testing, the direct observation of urination by same-sex observers, the use of bluing agents in toilet bowls, observing the urine color, and the measuring of urine temperature, pH, and specific gravity are a product of this experience. The following is an example of the diligence recommended by substance abuse experts in collecting the urine specimens:

> The collector must watch the client urinate. To obtain the best view of the female's urethra [sic] meatus, the collector can ask her to bend over and view the process from behind her. It is important to view the urine actually coming from the meatus and into the empty collection container, for both men and women.[22(p25)]

This type of procedure was recommended because skilled substance abusers have been known to strap bags of urine under their arms with tubing leading down their hands, making it difficult to distinguish whether the urine specimen is coming from the urethral meatus or the small tube.[22] Although few can argue about the use of bluing agents and the measuring of the physical properties of urine, the issue of the direct observation of urination is appropriately controversial. Is the war on drugs worth the kind of familiarity that the procedure recommended by Andersen and co-workers breeds? That is a question the policymakers will have to answer.

Rational drug testing programs attempt to balance the need for accuracy of the process with the need to preserve the rights and dignity of the people being tested. The federal government's approach to drug testing is basically consistent with this concept. As an example, the US Department of Transportation (DOT) regulations prescribe the specifics of how urine specimens are to be collected, the informing of the specimen donor of the process to which he or she will be subjected, and the certification of laboratories by the National Institute on Drug Abuse (NIDA); these specifics are an effort to assure that each collection site and each laboratory testing the urine of employees adhere to certain basic standards of quality control.

## The Role of the Physician in Urine Testing

The federal government approach, in an effort to avoid wrongly accusing an employee of illicit drug use, relies on a policy that includes placing a physician between the drug testing laboratory and the employer.[23] The physician functioning in this role, called a medical review officer (MRO), must be a licensed physician who has knowledge of substance abuse disorders and who has appropriate medical training to interpret and evaluate positive test results.[23] The medical review officer reviews positive urine drug tests that have been subjected to both screening and confirmation tests with the objective of determining whether there could have been a possible alternate medical explanation. The DOT regulations require that regulated industries conducting drug testing programs use a medical review officer. Consequently, many physicians will be asked by local companies, transit authorities, or governmental agencies to play a role in their drug testing programs. For some, this will be a familiar role, but others will find it unfamiliar. Given the primary forensic function of the medical review officer, many physicians may wonder if it is even appropriate for physicians to function in this capacity.

Some physicians will have ethical qualms about the MRO function, believing it does not constitute a true clinical function for a physician. A clinical rationale for physician participation might be that rehabilitation of the drug abuser would result. As McNeely points out, however, many drug testing programs are not linked to drug rehabilitation and are designed only to search for illicit drug use.[7] Hence, it could be argued that the MRO function is a police function rather than a clinical one. Yet, the thrust of the federal policy, as articulated by DOT regulations, appears to be to use a physician as a safeguard against wrongfully accusing a person of drug use. The DOT regulations that spell out the MRO function were chosen because the regulated employers are both private and public; the effective date was January 2, 1990. More than 4 million employees and 200,000 entities are affected by the DOT regulations. Six Department of Transportation agencies have promulgated regulations on drug testing programs: Federal Aviation Administration, Federal Highway Administration, Federal Railroad Administration, United States Coast Guard, Urban Mass Transportation Administration, and Research and Special Programs Administration.[23] Furthermore, regulated entities will be conducting preemployment, periodic, postaccident, reasonable cause, random, and return-to-duty drug testing. Thus, many physicians will be approached to serve as MROs, either in their capacities as employees of a regulated industry or as a contract employee.[24]

An MRO is not supposed to rubber-stamp the confirmed positive test reported by a laboratory. If an employee has a legitimate medical explanation for a confirmed positive drug test, the test will be reported to the employer as negative;

thus, the employee does not have to suffer the indignity of being accused of having used illicit substances.[25] An example of a situation where a laboratory reports a confirmed positive and the MRO reports a negative is with the use of topical cocaine by either a dentist, oral surgeon, or ophthalmologist; an employee unaware of the use of cocaine by the specialist provides a urine specimen for testing as requested and vehemently denies the use of cocaine when the urine tests positive.[26] (It is important to note that this is not an example of a false-positive on the part of the laboratory. Indeed, the employee has had exposure to cocaine but in a medically appropriate manner.) Without the appropriate inquiry into the circumstances of cocaine use by someone with medical knowledge, the employee's denial of such use would be met with knowing contempt, as many people who are confronted with evidence of drug use deny that use. All the MRO need do is to verify that indeed the visit to the specialist occurred and that the drug cocaine was used during the procedure at a time sufficiently close to the provision of the urine specimen to account for the confirmed positive drug test; thus, the result is reported to the employer as negative.

If an employee has a confirmed positive test and does not have a legitimate medical explanation, the test is reported to the employer as positive. This verified positive test means that an employee has had an opportunity to explore with the MRO possible explanations for the laboratory-confirmed results. An example of the MRO's role here would be wherein an employee tested positive for opiates and denied their use; the MRO on exploring drug use might elicit from the employee the taking of his or her spouse's prescription of Tylox for bursitis. The MRO would verify the laboratory's confirmed positive but would provide the employee with the information that Tylox contains oxycodone hydrochloride, a synthetic opiate. The verification occurs even if the employee denies knowledge of the content of the preparation and can establish that the spouse had a legally acquired prescription, since this was not the employee's prescription.

The conceptual role of the MRO is important. There may be physicians who envision their role as broad and sweeping; such physicians may identify too closely with the war on drugs, adopting a police posture rather than a more narrow review and interpretive posture. A role more broadly conceived than is prescribed by the regulations should be discouraged. The activities of the MRO conducted under DOT regulations must conform with the requirements of those regulations. Activities by physicians not explicitly sanctioned by the regulations will leave the physician vulnerable to negligence lawsuits for invasion of privacy and breach of confidentiality; the contracting or employing employer may also be subject to claims for hiring an MRO who acts beyond the permitted regulatory boundaries. For example, it is possible for an employee to test positive for morphine as a result of poppy-seed consumption. Here there is no prescription; should the MRO believe the employee? If the MRO does not believe the employee, and there is no rational basis for the belief such as track marks or acute behavioral changes, the MRO still must report the result as negative. If the MRO goes ahead and reports the confirmed positive as positive, this action is beyond the regulatory boundary.

On the other hand, physicians must take great care not to advocate for the patient in this situation. Implicit in the MRO function is a highly technical, almost neutral role. Again, the basic task of the MRO is to determine if there is a legitimate medical explanation for the confirmed positive urine test result. Therefore, assuming that the documentation is all in order and there is no suggestion of scientific insufficiency, the MRO can only base an opinion on existing medical knowledge at the time of the interpretation of the confirmed positive urine test collected and conducted according to the principles delineated in the regulations. As stated in the Tylox example, the fact that an employee claims to have used his or her spouse's medication for even a time-limited condition cannot sway the MRO from the primary task. The test is confirmed positive for opioids; the specimen donor has no prescription; therefore, the test is verified positive. Some physicians may object to this hard-and-fast procedure, but for an MRO to be effective in the long run, clear-cut procedures should be followed.

Peat points out that the drug testing of urine for nonclinical purposes is different in that it is not used in conjunction with other medical tests to assist in diagnosis.[12] Thus, a physician functioning as a medical review officer does not have the clinical support that normally attends the diagnostic process. In addition, the physician is not usually diagnosing a status or condition such as delirium or intoxication in the drug testing process, unless the MRO is the same physician by whom an employee is being seen for clinical assessment as a part of a for-cause assessment. The federal regulations limit the MRO to the one specimen tested, permitting at the most a retest of the same specimen by a different NIDA-certified laboratory.

At this time, there is no specific training for medical review officers for interpreting urine toxicology screens. Thus, there is no specific requirement for certification as an MRO. The federal regulations do not specify that the MRO should be an addiction medicine specialist, an occupational or industrial medicine specialist, a clinical toxicologist, a pharmacologist, or a laboratory medicine specialist. The regulations only require a medical license, a knowledge of substance abuse, and a knowledge of possible alternate medical explanations for a positive urine drug test result.

## Medical Review Officers' Tasks

On receiving from an employer's drug testing laboratory the confirmed results of a positive urine drug test, the MRO must review and interpret the results. This interpretation is based on a medical interview and review of the employee's medical history, a review of any other relevant biomedical factors and all medical records, or both.[27] This review process must include all medical records made available by the tested person when a confirmed positive test could have resulted from legally prescribed medication[27]; this means that for a drug such as phencyclidine, no medical records need be accepted from the employee because there is no known medical use for it. In addition, before making a final determination to verify the confirmed positive test, the MRO must give the tested employee an opportunity to discuss the test result.[28]

US Department of Transportation regulations require special attention for the opioid class of drugs. Before an MRO verifies a test confirmed positive for opiates, he or she must determine if there is clinical evidence, in addition to the urine test, of an unauthorized use of any opium, opiate, or opium derivative. The DOT regulations provide for ignoring this regulation only if the employer's laboratory confirms the presence of 6-monoacetylmorphine, a heroin metabolite; thus, it is clear that clinical evidence is important when it

comes to the prospect of heroin users, unless a metabolite that can only come from heroin is present. This clinical evidence must reach beyond mere prescription and medical record verification.[29] Track marks are mentioned in the handbook that DOT provides for MROs.

## The MRO's Knowledge

The MRO must also be knowledgeable about questions of accuracy and validity of a positive urine drug test. Under DOT regulations, only the MRO can authorize a retest of the specimen based on questions of accuracy and validity. Furthermore, the MRO must be able to determine if a confirmed positive is scientifically insufficient for further action, a conclusion that declares a test negative. For the MRO to declare a test specimen scientifically insufficient, the MRO must be able to assess inspection reports, quality control data, the results of multiple tests, and other pertinent conditions.[30]

A medical review officer, then, must have some expertise and familiarity with the drug testing process and the literature associated with drug testing. The MRO must know the meaning of such concepts as screen positive, screen negative, confirmed positive, confirmed negative. The MRO should know what process is used to screen the urine specimens and what process is used to confirm the result. For instance, the DOT regulations permit immunoassay screening but require gas chromatography-mass spectrometry (GC-MS) confirmation.[31]

Furthermore, the MRO must know the meaning of the concept of cutoffs used by the laboratory to report the results of their tests. A laboratory reports a test as positive because the specimen contains an amount of drug equal to a certain threshold concentration. The threshold concentration, also know as the cutoff, differs from the concept of sensitivity or detection limits of the methods involved; thus, sensitivity refers to the lowest concentration of a drug that can be detected.[32] The cutoff is usually higher than the detection limit because fewer errors will occur at the cutoff than at the detection limit, and fewer false-positives will result. The concept of cutoff for major urine screening programs has two basic applications: the lower limit of reliable testing based on the techniques involved in the testing and the lower limit of reliable testing based on the possibility of interference from medications, foodstuffs, environmental exposure, or endogenous processes. For example, the detection limit for cannabinoid radioimmunoassay is between 1 and 5 ng per ml, but the manufacturer's cutoff is set at 20 ng per ml.

Because a two-step process is required by the federal government in its urine testing programs and recommended by most authorities, the MRO must know that there are two sets of cutoffs involved in the urine drug testing process.[23] The DOT screening cutoff by immunoassay for marijuana metabolites is 100 ng per ml, but the confirmation cutoff by GC-MS is 15 ng per ml.[13] The screening test for marijuana screens for multiple metabolites, but the confirmation test is specific for one metabolite. Using marijuana as an example again, GC-MS tests for $\Delta^9$-carboxytetrahydrocannabinol (THC); thus, despite the fact that there are 100 ng per ml of cannabinoid metabolites in a screening specimen, there must be at least 15 ng per ml of $\Delta^9$-carboxy-THC present before the laboratory can report a confirmed positive.

For the DOT regulations, there are those who think that certain cutoffs should be lower than they are, arguing for a screen-positive concentration of 20 ng per ml for marijuana instead of 100 ng per ml, 500 ng per ml for amphetamines instead of 1,000 ng per ml, and 150 ng per ml for cocaine instead of 300 ng per ml. The rationale offered for the lowered levels is that more people using drugs would be caught.[23] The US Department of Transportation wisely chose a conservative route by maintaining the cutoffs as they are for two reasons: smaller quantities of metabolites are treated as negatives, avoiding the complications of cross-reactivity and interference by food products and passive exposure, and program costs are lower with the higher cutoffs. The MRO should know that these cutoffs are to some degree arbitrary and can be raised and lowered depending on new information and new technology (Table 1).

Urine specimens collected under the auspices of the DOT regulations will currently be tested for only five drugs: marijuana, cocaine, opiates, phencyclidine, and the amphetamines (including methamphetamine).[33] Thus, the MRO must be familiar with the properties, pharmacokinetics, metabolism, and legal uses of these drugs. Of the five drugs, only phencyclidine has no current medical use. There are those who would have the MRO test for a wider range of substances, adding to the list of five at least the following: alcohol, benzodiazepines, barbiturates, and methaqualone. Obviously, any MRO operating with this expanded list should have a substantive familiarity with these drugs. Only methaqualone on this additional list is clearly illegal; all other drugs may have legal uses.

## NIDA and DOT Manuals

The National Institute on Drug Abuse and the US Department of Transportation have both published booklets to guide MROs.[34,35] These booklets provide an overview of the perceived function of a medical review officer. The DOT manual does track, however, the DOT regulations, which gives MROs a specific approach to executing their function. The NIDA manual contains a graph of a decision tree that a physician would follow in decision making. Both manuals review the types of tests, the testing procedure, the assays that may be used, and an overview of the drugs that are prohibited.

TABLE 1.—*US Department of Transportation Testing Requirements*

| *Drug* | *Cutoff Level, ng/ml* |
|---|---|
| Screening test (immunoassay) | |
| Marijuana metabolites | 100 |
| Cocaine metabolites | 300 |
| Opiate metabolites | 300* |
| Phencyclidine | 25 |
| Amphetamines | 1,000 |
| Confirmatory test (GC-MS) | |
| Marijuana metabolite† | 15 |
| Cocaine metabolite‡ | 150 |
| Opiates | |
| Morphine | 300 |
| Codeine | 300 |
| Phencyclidine | 25 |
| Amphetamines | |
| Amphetamine | 500 |
| Methamphetamine | 500 |

GC-MS = gas chromatography-mass spectrometry

*25 ng/ml if immunoassay specific for free morphine.
†$\Delta^9$-Tetrahydrocannabinol-9-carboxylic acid.
‡Benzoylecgonine.

Both manuals include a table that summarizes options in complex opioid-positive cases. The DOT manual has a specific section on the MRO review process and standard operating procedures that evolve from that process. The NIDA manual has a special section on proper prescriptions and on opiates.

The manuals, however, can be deceptive to an unsuspecting physician; their blind use projects an image of cookbook decision making in interpreting the confirmed positive results. Any physician who thinks that the process can be reduced to a simple chart is risking extreme liability. Furthermore, the manuals are only a guide; they do not substitute for the practice of medicine. In any event, there is at least one possible contradiction between the manuals and the response to the comments published with the final rule for DOT.

US Department of Transportation commentators and the DOT manual note that an MRO need only conduct a telephone interview with an employee who tested positive.[23,35] Both the regulations themselves and the DOT manual, however, subsequently say that if a person tests positive for opiates, clinical evidence must be taken into consideration, unless the laboratory test involved tests for the presence of 6-monoacetylmorphine. Both the DOT and NIDA manuals point out that the clinical evidence includes recent needle tracks and behavioral signs of acute opiate intoxication or withdrawal; this clinical evidence is difficult to verify over the telephone. Medical review officers who are not prepared to actually examine opiate-positive persons can only guess at whether the positivity is from heroin or some other source. An enterprising addict replete with new track marks will simply state in a telephone interview that poppy-seed cake is the source of the positive result; without an actual examination, the MRO is forced to report the result as negative. If such an employee is subsequently involved in an accident, the MRO will be on record as having provided a negative report for someone who with a little diligence would have easily been verified as positive. Third parties will attempt to hold the MRO liable for any harm suffered by them based on the MRO decision not to examine an affected employee; this is especially applicable to operators of large vehicles such as trucks, buses, or trains.

## MRO Standard Operating Procedure

Critical to the functioning of an MRO is an understanding of the authorizing regulations. (In situations where the urine testing is being conducted without the auspices of federal regulations, there must be clearly defined rules for the MRO and a clear understanding of what is expected of the MRO and to whom the MRO reports.) The DOT manual, under the section, "Standard Operating Procedure," summarizes the authorizing regulations succinctly. Ideally, an MRO should have a copy of both the DOT's manual and the authorizing regulations and be familiar with both. The MRO should develop his or her own set of standard operating procedures, especially if staff will be assisting in the process of contacting employees or in executing an initial medical history (a function permitted to medically licensed or certified staff).[36]

The DOT manual prescribes a three-step process for carrying out the responsibilities of the MRO: the receipt of laboratory test reports, positive test report-verification process, and reporting of a verified positive test result. In each step, there are instructions for the MRO's conduct. The MRO should pay close attention to these instructions and follow the process. The second and third steps offer the greatest potential for mischief and error; thus, they will be discussed further.

### *Immunoassay Negative Reports*

The MRO's treatment of negative results is administrative. This means that the MRO or the MRO's staff must simply check the chain of custody documentation received from the laboratory and forward negative results to employers. The MRO also stores the documentation of these findings. Thus, the MRO is not concerned about false-negatives. If there are reasons to think that a person is using drugs, outside of self-admissions, that are unsubstantiated by a urine test, the MRO's function qua MRO is not to pursue further exploration of those reasons. Nothing in the DOT regulations precludes this activity per se, but the regulations do state: "The duties of the MRO with respect to negative results are purely administrative."[37] Thus, while an agent of the employer, the MRO's role is basically restricted to interpreting and reviewing positive test results.[27]

### *Positive Test Report-Verification Process*

The MRO must

- Review positive report documents
- Notify employees of positive test results
- Provide an employee an opportunity to discuss the test result
- Review medical records
- Review medical history and other biomedical factors
- Process employees' requests for retesting
- Authorize testing of a "split specimen" for drug metabolites.

The last two will not be discussed in this article, as they are technical and uncomplicated; the MRO should turn to the regulations or the MRO manuals to address these items.

While an MRO under DOT regulations receives both positive and negative results from laboratories, the primary and most important role for the MRO is in the area of positive test results. The physician must remember at all times that the MRO role is a forensic one. The physician should also understand that the MRO is an agent of the employer, not of the employee tested; for those whose clinical experience is limited to providing services directly to patients, with the patient being the focus of care, this role may produce conflict.

## The Limits of Confidentiality

Before pursuing other aspects of the procedures that an MRO may use under the DOT regulations, the MRO must consider significant exceptions that appear in the regulations around the issue of confidentiality. The regulations proscribe disclosure of the specimen donor's medical information except for the following circumstances. The regulations permit the MRO to disclose medical information to the employer, a DOT agency or other federal safety agency, or the physician who determines the medical qualifications of the specimen donor under DOT regulations if

- An applicable DOT regulation permits or requires such disclosure;
- In the MRO's reasonable medical judgment, the information could result in the employee being determined to be medically unqualified under an applicable DOT agency rule; or

• In the MRO's reasonable medical judgment, in a situation in which there is no DOT agency rule establishing physical qualification standards applicable to the employee, the information indicates that continued performance by the employee of his or her safety-sensitive function could pose a major safety risk.[38]

These exceptions to confidentiality create a special problem for MROs; they potentially broaden the MRO function beyond the mere role of reviewing and interpreting positive urine drug tests. Consequently, the MRO must weigh the implications of these exceptions before and during the primary medical reviewing task. The MRO should note that these exceptions are discretionary; by being discretionary, the MRO can choose not to disclose. With discretionary functions, however, the MRO will have to have a reasonable basis for disclosing or not disclosing, especially in the third exception. Note that the regulations apply to medical information, not just to a confirmed positive drug test.

The first two optional exceptions to confidentiality require that an MRO have knowledge of the applicable DOT regulations that govern the disclosure of medical information, the medical qualification of regulated employees being tested, or both. Thus, MROs who serve a spectrum of industries might be required to be familiar with the medical qualifications of the aviation, motor carrier, railroad, maritime, mass transit, and pipeline industries. The second exception requires an MRO to make a reasonable medical judgment about whether the information that is discovered in the medical files or information that the employee submits for scrutiny would result in an employee being determined medically unqualified under applicable DOT regulations. An example of this second exception might be that in reviewing the medical records of a pilot with a first-class medical certificate who tested positive for codeine following the treatment of a bad cough by a local physician, the MRO finds references to chest pain that responded to the use of nitroglycerin. The Federal Aviation Administration-DOT regulations require that a holder of a first-class medical certificate have no established medical history or clinical diagnosis of myocardial infarction, angina pectoris, or either symptomatic or treated coronary artery disease.[39] By receiving all the medical records, the MRO now has to make a decision: to disclose or not to disclose.

It is in the third exception to the regulation governing confidentiality that the prospect of third-party liability is clearly established. In this exception, knowledge of the rules of DOT is irrelevant. If the MRO knows something about the specimen donor's job and discovers medical information that suggests that continued performance of a safety-sensitive job could pose a significant safety risk, the MRO has the option to disclose. Clearly that option here is really an obligation. The MRO would have to have an extremely solid reason for not disclosing, as the regulation requires the exercise of "reasonable medical judgment." Reasonable medical judgment becomes a standard in a negligence lawsuit against the MRO who fails to disclose information that a particular employee is a safety risk. Oddly enough, the original physician who actually examined and treated the affected employee may have no obligation to disclose the same information to the employer, any federal agency, or the employer's screening physician. In those situations where the primary physician may be held liable for a failure to warn a patient or failure to protect the public,[40] the MRO may simply become a backup defendant; plaintiff's attorneys can use the "reasonable medical judgment" standard created by the regulations as a basis to convince a jury.

In any of the exceptions to confidentiality permitted by the regulations, decisions to disclose made without a face-to-face interview risk provoking the anger and rage of the employee. An employee may feel tricked and deceived by the MRO and the employer. If the drug testing program is perceived as a device to discover the medical records of an employee, the MRO and the employer may suffer subsequent litigation. More important, employees will view the drug testing program not as an effort to stop the use of drugs in the workplace but to probe into the private medical life of the employee; this view will encourage subversion of the drug testing program. The MRO, therefore, may choose to establish procedures that militate against the surprise of an employee who tests positive for a legally acquired drug but whose medical records may contain material that suggests the need to breach the employee's confidentiality.

## Notice to Employees

First, before a medical review officer initiates contacting a specimen donor who has a confirmed positive specimen, there must be a clear understanding of legal issues in the DOT process. Before obtaining medical information from the employee as a part of the verification process, the MRO must notify the employee of the potential for the disclosure of medical information to third parties.[41] This is required by regulation. Consequently, the MRO must have decided beforehand just who those third parties are to be. Furthermore, the MRO should inform the specimen donor that the medical information disclosed may not have anything to do with the confirmed positive urine test.

Second, the MRO may choose to tailor requests for medical information to the specific drugs for which the employee tested positive. Hence, the MRO could request that the employee have his or her prescribing physician send documentation of only the prescription involved or the medical procedure involved. By restricting the focus of the inquiry, the MRO decreases the chance of discovering other information that has nothing to do with drug testing. This may appear to some as an evasion of an obligation, but, as stated, the test-positive employee comes to the MRO only for the reason of the drug test, not for a routine physical examination and not for the assessment of a medical condition. The employee's workup could be incomplete, in progress, or in error. The MRO would have only the documents to guide the decision making, especially if the entire contact with the employee occurs over the phone and through the mails. Thus, the MRO would have to second-guess the primary practitioner to determine if the employee specimen donor were indeed a safety hazard or not medically qualified for his or her job.

Both the DOT and the NIDA manuals provide information about legitimate positive test results. The DOT manual states simply that there are four principal explanations for a legitimate positive test result: (1) Errors in the laboratory process, (2) errors in the "chain of custody," (3) legally prescribed or dispensed medications, and (4) legally acquired foodstuffs or other substances that produce the same metabolites as illegally acquired substances. Items 3 and 4 are most easily the major items that the MRO will be evaluating. While items 1 and 2 may occur, it is assumed that their frequency will be low. There is one situation, however, that

could be subsumed under item 1 in this paragraph that needs to be discussed, and that is the issue of Vicks nasal inhalers.

Vicks Inhaler contains the legal ingredient, desoxyephedrine, or *R*(−)-methamphetamine, which can test positive for methamphetamine on immunoassay and on GC-MS. Fitzgerald and colleagues showed that a person inhaling from a Vicks Inhaler every 20 minutes for six hours can test positive for the illegal *S*(+)-isomer.[42] They used an EMIT and TDx, types of immunoassays, with a cutoff of 300 ng per ml, which is much less than the 1,000 ng per ml cutoff permitted by the DOT regulations; nevertheless, one subject had a peak urinary concentration of *R*(−)-methamphetamine of 6,000 ng per ml; this raises the prospect of a confirmed positive for a few persons who are heavy users of Vicks Inhaler either through abuse, through innocent misuse, or simply their idiosyncratic physiology. The only way to assess whether the confirmed positive is a true positive is for the laboratory to determine the optical isomers of the amphetamine; with the isometric composition of methamphetamine determined, the probable source of the drug may be determined. Thus, a medical review officer would be negligent to verify a confirmed positive for methamphetamine without having access to the optical isomers. Without the optical isomers, an employee with no prescription for methamphetamine but with a statement of using Vicks Inhaler would have to be determined to be negative.

The MRO relying only on the NIDA or DOT manuals (or both) would find no reference to the article by Fitzgerald and associates. Nevertheless, the issue of a test that is false-positive for methamphetamine is real. Unless other researchers are able to challenge the findings of Fitzgerald and coworkers, their article must stand as the standard on the question of whether Vicks nasal inhalers can produce a false-positive result for methamphetamine. Without the MRO knowing that a repeat laboratory study is required to inquire about the question of optical isomers, great harm could come to the specimen donor. Furthermore, it is not clear that DOT regulations permit isomeric differentiation. In a lawsuit, the MRO would be more than embarrassed by an error caused by this ignorance. The MRO is supposed to have the knowledge and skills to interpret these tests—this is required by regulation. It would be a poor defense in a malpractice trial to assert that the question of Vicks nasal inhaler was not covered in either the NIDA or DOT guidebooks.

## Review of Chain of Custody Documents

It is critical that the MRO review the chain of custody documents that are received from the laboratory. This function is important for both screening-negative and confirmed positive urine results. While the screening-negative specimens can be handled administratively, the MRO or staff must ascertain that the chain of custody documents are in order. This review of documentation is clearly important when an employee is to be informed that he or she has a confirmed positive test result. Standard procedures should be developed by the MRO for the staff to verify appropriate documentation

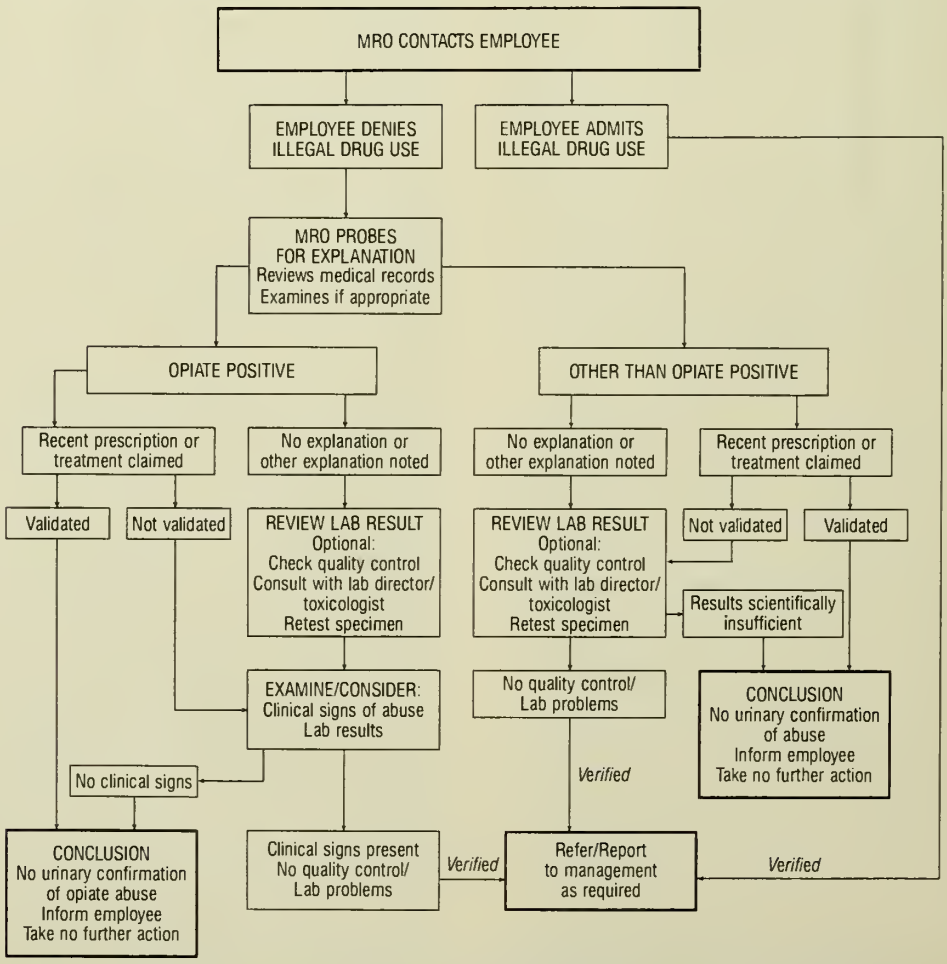



**Figure 1.**—A decision tree is shown for a medical review officer's (MRO) review and action for a urinalysis positive for drugs (from the National Institute on Drug Abuse).[34]

that comes from the laboratory. Again, this should not be a significant source of error, but if there are errors, they will not be detected if the MRO has no systematic approach to this matter.

## Legitimate Medical Explanations

As stated, legally prescribed or dispensed medications or foodstuffs that produce the same metabolites as illegally acquired substances constitute a principal basis for reporting a confirmed positive urine test as negative. The NIDA manual includes a decision tree for the MRO review and action (Figure 1). Both the NIDA and the DOT manuals include charts to assist in the conclusions in complex opioid cases (Table 2). These aids are useful for a physician who is formulating a standardized approach to decision making for confirmed positive urine tests.

As indicated, these decision trees and decision manuals are not a substitute for medical decision making. An absolute reliance on such material may lead to conflicts for employees tested, the employers, and the physician. An example of the limitations of standardized material would be the described case of a positive test for methamphetamine. The NIDA and the DOT manuals indicate that the screening tests cross-react for various amphetamine-related compounds; however, both manuals state that GC-MS confirmation distinguishes the cross-reacting compounds, assuring that final reports that are received by the MRO are not false-positives. Neither manual mentions the over-the-counter preparation Vicks Inhaler, however. In addition, the drug L-deprenyl (selegiline), a monoamine oxidase type B inhibitor used in the treatment of parkinsonism, is reported to produce isomers of amphetamine and methamphetamine that are excreted in the urine; these isomers are thought to be the $R(-)$ type found in Vicks Inhaler.[43] While it is not likely that more than a few employees will ever be taking this drug, mass screening of the working population may involve some of those on deprenyl therapy. In reality, all the permutations of drug testing and conflicting drugs have not been properly worked out. The MRO must keep abreast of the clinical and toxicology literature. As a result of a faulty MRO decision, a person may be denied a job, fired, or mandated into a treatment process that is unnecessary and undesired. As mentioned previously, the interpretations here, unlike other clinical settings, are primarily based on a single urine specimen.

The academic and clinical literature can help medical review officers understand the drug testing process. Four articles are recommended here to aid them in achieving an overview.[13,15,17,32] Despite the fact that these articles are recommended, they are not definitive. Kelly's article, for example, reflects the contamination of science by the war on drugs policy; for instance, on the subject of the passive inhalation of marijuana smoke, she cites a study by Cone and associates, saying, "While several urine tests were positive for cannabinoid at the 20 ng/ml cutoff, the conditions were so extreme that the subjects had to wear goggles because of eye irritation."[17] What Cone and co-workers actually wrote was

> Our subjects were instructed to wear colored eye goggles throughout the smoke-exposure in order to prevent color discrimination between placebo and active marijuana cigarettes and to prevent eye irritation from smoke. Most subjects followed these instructions but some removed them for short periods of time while the cigarettes were burning. Based on their comments, it seems unlikely that exposure to the smoke of 16 marijuana cigarettes without eye goggles would have been tolerable for most subjects for extended periods of time.[44(p95)]

Kelly, who works for the makers of the EMIT process, appears to have been distracted by Cone and colleagues' impressions. Because Kelly's article is a review, it should have

TABLE 2.—*Medical Review Officer's (MRO) Conclusions in Complex Opioid Cases*

| | Employee | | | |
|---|---|---|---|---|
| *Urinalysis Results* | *Presents Prescription* | *Claims Poppy-Seed Eating* | *Signs of Abuse* | *MRO's Conclusion of Probable Explanation* |
| 6-Monoacetylmorphine with or without other findings | NR | NR | NR | Urine test confirms heroin abuse |
| Morphine | Morphine sulfate | NR | NR | No urinary confirmation of opioid abuse |
| Morphine | None | Yes | Yes | Urine test confirms heroin or morphine abuse |
| Morphine predominates, some codeine | Morphine sulfate | NR | NR | No urinary confirmation of opioid abuse |
| Morphine predominates, some codeine | Codeine | No | Yes | Urine test confirms morphine or heroin abuse |
| Morphine predominates, some codeine | Codeine | Yes | NR | No urinary confirmation of opioid abuse |
| Codeine predominates, some morphine | Codeine | NR | NR | No urinary confirmation of opioid abuse |
| Codeine predominates, some morphine | None | Yes | Yes | Urine test confirms codeine abuse |
| Codeine predominates, some morphine | None | Yes | None | No urinary confirmation of opioid abuse |
| Negative | None | No | Yes, extreme | No urinary confirmation of opioid abuse |
| Hydromorphone HCl (Dilaudid) | None | Yes | None | Urine test confirms hydromorphone abuse |
| Methadone | Methadone HCl | No | Yes | No urinary confirmation of opioid abuse |
| Methadone and morphine | Methadone HCl | Yes | Yes | No urinary confirmation of morphine or heroin abuse |
| Methadone | None | Yes | NR | Urine test confirms methadone abuse |

HCl = hydrochloride, NR = not relevant

noted that Cone and associates did not assess or measure the amount of smoke in the atmosphere of the room or the degree of irritation on the eyes of the subjects but based their conclusions only on the comments of a nondescript "some" of the seven subjects in the study population. Just how extreme the conditions would need to be before a person could not tolerate atmospheric marijuana smoke is not clear. Cone and co-workers could have used the smoke from tobacco cigarettes as a comparison or measure of eye irritation. In addition, their work did not address the question of what happens when both tobacco and marijuana cigarettes are being smoked in the same room. The issue of marijuana smoke is important because of the lingering question of passive inhalation. An MRO may be asked by an employer or employee assistance program person if an employee with a low titer of THC metabolite could have been a passive inhaler; this question is not answered by either Cone and associates' study or Kelly's review. This may seem a minor point, but it underscores the problem confronting MROs. Much of the literature is biased either for or against urine testing. This bias creates a credibility problem and a liability problem, given that most MROs will not have any actual research experience in urine drug testing. Nevertheless, the four articles mentioned, as well as the one by Cone and co-workers, are good background reading.

### Standard of Care

Given the potentially grave consequences of faulty interpretation, enterprising attorneys undoubtedly will push for a stricter standard than the regular practice of internal medicine, occupational or industrial medicine, or family practice. Standards based on the expertise of specialists in pharmacology, toxicology, or addiction medicine would be demanded. Such standards would be justified, given the risks for specimen donors involved and given that the justifying regulations require a reasonable knowledge of information shared by those specialties.

How a medical review officer will keep abreast of changing toxicology and substance abuse issues is not currently clear. Subscribing to mainstream toxicology and clinical laboratory journals that carry research about the various methods, their potentials, and their limitations should be helpful. Addiction medicine literature and pharmacology literature will undoubtedly carry more information about the usefulness and pitfalls of urine testing. Attending periodic continuing education courses in the area of substance abuse and urine testing for drugs of abuse should also help. With the passage of time, there should be newsletters circulating to physician-MROs highlighting changes in the body of knowledge. Perhaps NIDA, DOT, or another federal agency will take the lead in creating a clearinghouse to keep subscribing MROs apprised of this information; this would be ideal, given that the urine testing regulations under which MROs are operating are federally promulgated, and NIDA, DOT, or both might publish more frequent updates of their manuals as clinicians in the field acquire more experience through the large-scale testing being conducted.

At least one DOT agency, the Federal Aviation Administration, has sponsored a seminar on the role of medical review officers. While tailored for the aviation MRO, the day-and-a-half seminar covers the regulations, the specimen collection procedures, pharmacologic aspects of the five drugs tested, laboratory and toxicology issues, and the duties and responsibilities of an MRO. The agency also publishes its own MRO guide.[45] In addition, there is at least one proprietary course on the role of MROs (Employee Health Programs, 1825 Eye St, NW, Ste 400, Washington, DC 20006).

### On Fees and Time

A physician functioning as an MRO must realize that stepping into the role of assessing the legitimacy of an employee's prescription or food consumption is not the same thing as doing a certifying physical examination for a license. The standard of care, then, must be that reasonable level of care that should be given in the situation. Because of cost considerations, many companies will pressure physician contractors to perform the MRO service at the lowest fee. Fees set too low, however, will encourage physicians to be too quick or careless in the assessment of a confirmed positive urine test. Flat fees, as in capitation, must take into consideration epidemiologic aspects of drug use in the employee population tested: a low prevalence of drug use permits a low capitation fee based only on the administrative costs; a high prevalence of drug use suggests a fee-for-service basis because of the uncertainties of how much time a given employee's case will require. Caution must be exercised not to deny an employee as much time as is required to establish whether a confirmed positive test should be verified. Thus, streamlining the interview process for the sole purpose of saving time and money should be discouraged.

### Documentation and Records

Medical review officers must have careful documentation on each confirmed positive case reviewed. From the moment of contact to the moment of reporting, a written record should reveal the character and the content of each transaction. This documentation can be organized around a record flow chart or questionnaire set. However it is completed, the documentation should permit a plaintiff's attorney to understand the procedures employed and the reasoning used to make the decision. Using the chain-of-custody approach, the MRO should establish sign offs for each step. If a secretary or nurse first contacts the confirmed positive employee, the time and date should be recorded and the signature of the contacting staff person should be clearly legible. The MRO should also document his or her interactions with the person with a confirmed positive test: this includes time and date of interview, the substance of the interview, releases of information signed by the employee to talk with health care practitioners, a list and time of receipt of documents from corroborating health care practitioners, a summary of the decision-making process, and when the decision, either negative or verified positive, was sent to the employer or other agency. Each folder, then, should be a litigation package that should also serve as a memory jogger for the MRO in the event of litigation or arbitration.

### Reporting a Verified Positive Test Result

Once a confirmed positive report has been verified by the MRO, the result must be reported to the employer. Employers may choose the policy that they want to follow, however. Some MROs may report to the employer's employee assistance program; others may require that the employee be directed to a designated rehabilitation program. Still others may simply request that the MRO report to a designated management official who would handle the management of

the employee's situation from that point on. Whatever the procedure, the policy should be clear and written so that the MRO does not disclose private information to the wrong person. In addition, the MRO must possess knowledge about the rehabilitation process and community resources.

Medical review officers should understand what options are available under the insurance plans offered by the employers for whom they work. They should also know which public programs exist in their community so that they can refer employees who are not insured to these facilities. Because the MRO may be required to review the urine specimens of employees who are reentering employment following a period of rehabilitation, he or she may prefer to recommend to the employer or to the employee assistance program that a formal monitoring and reentry program be involved. These programs routinely have participants produce urine specimens for drug testing and evaluate those specimens. In situations where no physician is available to interpret drug tests, the MRO may work with the monitoring and reentry program as a part of helping the employee return to duty.

## Return-to-Work Recommendations

Work with rehabilitation counselors through monitoring and reentry programs is critical, as US Department of Transportation agency regulations may require a medical review officer to make a recommendation on when an applicant or employee may be hired or permitted to return to duty in a security or safety-sensitive position. The DOT manual points out that the MRO must obtain from the rehabilitation counselor an assessment that includes the nature and degree of a person's past substance abuse, progress in any rehabilitation effort, and the prognosis and recommendations concerning recommended aftercare services.[35] Upon reviewing the rehabilitation report, the MRO must also be satisfied that the employee complied with the conditions and requirements of the rehabilitation program in which he or she participated. In addition, the MRO must determine that a return-to-work urine specimen is drug-free, showing no evidence of any current drug use. Then the MRO makes a return-to-duty recommendation. If the MRO recommends that an employee return to work, he or she must also establish a schedule for random, unannounced drug tests based on the assessment and recommendation of the rehabilitation counselor.[35]

It is clear, then, that the role of the MRO in return-to-duty recommendations requires a combination of skills: clinical pharmacology, laboratory medicine, addiction medicine, and occupational or industrial medicine. It is also clear that a physician undertaking MRO functions must exercise great care in making the appropriate determination. For instance, while the rehabilitation program may make recommendations, employers rely on the MRO's assessment to decide whether an employee returns to work. If the MRO is unfamiliar with drug treatment and recommends that an employee return to work prematurely, the liability cannot be shifted to the rehabilitation program. Concomitantly, if the MRO unreasonably prevents an employee from returning to work, challenges will occur in either arbitration or litigation.

## Physicians With Several Roles

Some MROs may have more than one role in their relationship with employees subject to testing. Conceivably, the MRO may be the certifying physician who determines that the employee is physically fit and the collection site physician who collects urine for the drug testing. In each of these roles, information is collected about the employee that requires record keeping. Although the MRO may be tempted to collapse the record of the employee into one central file, implicit in each role is a different set of responsibilities. Furthermore, the more roles that a physician has in a relationship with an employee subject to testing, the greater the potential for conflicts of interest and of loyalties. Physicians who are actual employees of a company are more easily identified as being the exclusive agent of the employer; physicians who are simply contracting with the employer may be confused by the employee as a more personal practitioner. Physicians who function as the MRO and in other capacities should take great care to avoid the appearance of conflict. The maintenance of function-specific records, kept and accessed separately, can serve to document the separate objectives of each function. Physicians with multiple roles should consult with attorneys conversant with the authorizing regulations and with the practicalities of their practice about the best method of record keeping; however, the employee subject to testing should have a clear understanding of the boundaries of each of the multiple roles.

## Conclusion

A number of details about the role and function of medical review officers are unaddressed by this article. This is not meant to be a definitive encyclopedic review of the function of the physician as a medical review officer, but it should be clear to physicians interested in the role of MRO that great care must be exercised in executing this decidedly forensic function. While some commentators have noted that laboratories are making substantial monies from the war on drugs (M. Freudenheim, "Booming Business: Drug Use Tests," *New York Times,* Jan 3, 1990, p C1), it should be clear from the above material that physicians will probably earn no more than they would from seeing a regular patient. Physicians should always remember that great care must be exercised in the MRO function because the decision making has outcomes that are almost immediate. Jobs and reputations ride on the skill and deliberations of the physician MRO.

Malpractice carriers will obviously look closely at the experience of physicians functioning as MROs. More so than the normal practice of medicine, the role of the MRO invites litigation. The MRO reviews and evaluates positive drug tests. Therefore, either there is a legal medical alternative or an employee will be subject to treatment, termination, or not hired, if a job applicant. Given the possible desperation that the situation of a positive drug test creates, legal recourse will be an almost instant reaction. Consequently, any deviation from the prescribed procedures of the regulations will create a cause for legal challenge. Any failure on the part of the MRO to keep abreast of contemporary literature and research that results in denying an employee a deservedly verified negative report will invite legal challenges. As mentioned, the medical community is far from united on the issue of widespread testing for illicit drugs; this is particularly the case because such substances as alcohol and nicotine are responsible for billions of dollars of health care costs and large-scale morbidity and mortality. This lack of uniform support will encourage specialists who are willing to serve as expert witnesses in malpractice cases where breaches of the standard of care are alleged.

Even in those situations where a person acknowledges the use of proscribed substance, the MRO must take great care in decision making and documentation. The MRO must keep scrupulous records; the forensic nature of the MRO function requires clear evidence of decision making. The MRO must resist pressures for rapid and premature conclusions. If errors are ineluctable, they should not be errors that could have been avoided by adequately interviewing the employee or by keeping abreast of the research that shows that a given drug cross-reacts with a proscribed one or produces metabolites that are otherwise prohibited.

Once in possession of medical information other than that directly related to the confirmed positive test result, the MRO must take great care in deciding how to manage that information. The employee may be encumbered by the careless disclosure of information about his or her health. On the other hand, the public has a right to require those who hold security or safety-sensitive positions to be capable and vigilant while on the job.

The controversy around the issue of urine testing continues to rage. Undoubtedly, as more of the public is involuntarily subjected to this procedure, the conflict over urine testing will escalate. Physicians cannot avoid this controversy, either because of the role of MROs or because they are prescribing medications for their patients that may produce confirmed positive test results. For the many reasons stated and unstated, it is critical that physicians appreciate the advantages and disadvantages of the concerted pursuit of the last nanogram of proscribed substances in the urine of Americans.

## REFERENCES


1. Hoyt DW, Finnigan RE, Nee T, et al: Drug testing in the workplace—Are methods legally defensible? JAMA 1987; 258:504-509
2. Lubran MM, Jasper KT: Drug abuse in the workplace. Ann Clin Lab Sci 1988; 18:6-12
3. Marshall E: Testing urine for drugs. Science 1988; 241:150-152
4. McCunney RJ: Drug testing: Technical complications of a complex social issue. Am J Ind Med 1989; 15:589-600
5. Bush G: National Drug Control Strategy—The White House. Government Printing Office, 1989
6. Glantz LH: A nation of suspects: Drug testing and the Fourth Amendment. Am J Public Health 1989; 79:1427-1431
7. McNeely E: Drug testing: Ethical considerations. J Am Assoc Occup Health Nurse 1988; 36:118,120
8. Canavan DI: Screening: Urine drug tests. Md Med J 1987; 36:229-233
9. Irving J: Drug testing in the military—Technical and legal problems. Clin Chem 1988; 34:637-640
10. Davis KH, Hawks RL, Blanke RV: Assessment of laboratory quality in urine drug testing. JAMA 1988; 260:1749-1754
11. Hansen HJ, Caudill SP, Boone J: Crisis in drug testing. JAMA 1985; 253:2382-2387
12. Peat MA: Analytical and technical aspects of testing for drug abuse: Confirmatory procedures. Clin Chem 1988; 34:471-473
13. American Association for Clinical Chemistry: Critical issues in urinalysis of abused substances—Report of the Substance Abuse Testing Committee. Clin Chem 1988; 34:605-632
14. Chamberlain RT: Legal issues related to drug testing in the clinical laboratory. Clin Chem 1988; 34:633-636
15. Schwartz RH: Urine testing in the detection of drugs of abuse. Arch Intern Med 1988; 148:2407-2412
16. Morgan JP: Marijuana metabolism in the context of urine testing for cannabinoid metabolite. J Psychoactive Drugs 1988; 20:107-115
17. Kelly KL: The accuracy and reliability of tests for drugs of abuse in urine samples. Pharmacotherapy 1988; 8:263-275
18. Mikkelsen SL, Ash KO: Adulterants causing false negatives in illicit drug testing. Clin Chem 1988; 34:2333-2336
19. Warner A: Interference of common household chemicals in immunoassay methods for drugs of abuse. Clin Chem 1989; 35:648-651
20. Cody JT, Schwarzhoff RH: Impact of adulterants on RIA analysis of urine for drugs of abuse. J Anal Toxicol 1989; 13:277-284
21. Goldsmith MF: Drug testing upheld, decried; physicians asked to help decide. JAMA 1988; 259:2341-2342
22. Andersen M, Albright K, Serowoky M: Collecting a reliable urine specimen for drug analysis. J Nurs Admin 1987; 17:25,32
23. Procedures for transportation workplace drug testing programs. Federal Register 1989; 54(230):49854-49884
24. 49 CFR §40.33(b)(1)
25. 49 CFR §40.33(f)
26. Bralliar BB, Skarf B, Owens JB: Ophthalmic use of cocaine and the urine test for benzoylecgonine. N Engl J Med 1989; 320:1757-1758
27. 49 CFR §40.33(b)(3)
28. 49 CFR §40.33(c)(1)
29. 49 CFR §40.33(d)
30. 49 CFR §40.33(g)
31. 49 CFR §40.29(e) and §40.29(f)
32. Saxon AJ, Calsyn DA, Haver VM, et al: Clinical evaluation and use of urine screening for drug abuse. West J Med 1988; 149:296-303
33. 49 CFR §40.21(a)
34. Medical Review Officer Manual, US Dept of Health and Human Services publication No. (ADM) 88-1526. Rockville, Md, National Institute on Drug Abuse, 1988
35. Medical Review Officer Guide for Regulated Transportation Industries. Washington, DC, Department of Transportation, 1989
36. 49 CFR §40.33(c)(2)
37. 49 CFR §40.33(a)(2)
38. 49 CFR §40.33(h)(1)
39. 14 CFR §67.13(e)
40. Lambert TF: Medical negligence: Doctor's liability to third persons. Assoc Trial Lawyers Am Law Report 1989; 32:446-449
41. 49 CFR §40.33(h)(2)
42. Fitzgerald RL, Ramos JM, Bogema SC, et al: Resolution of methamphetamine stereoisomers in urine drug testing: Urinary excretion of *R*(-)-methamphetamine following use of nasal inhalers. J Anal Toxicol 1988; 12:255-259
43. Karoum F, Chuang LW, Eisler T, et al: Metabolism of (-) deprenyl to amphetamine and methamphetamine may be responsible for deprenyl's therapeutic benefit: A biochemical assessment. Neurology (NY) 1982; 32:503-509
44. Cone EJ, Johnson RE, Darwin WD, et al: Passive inhalation of marijuana smoke: Urinalysis and room air levels of $\Delta^9$-tetrahydrocannabinol. J Anal Toxicol 1987; 11:89-96
45. The Aviation Medical Review Officer Guide. Available from the Drug Abatement Branch, Office of Aviation Medicine, Federal Aviation Administration, Washington, DC, 1990

**Addiction Medicine**
**and the Primary Care Physician**

# Pulmonary Complications of Smoked Substance Abuse

DONALD P. TASHKIN, MD, *Los Angeles*

*After tobacco, marijuana is the most widely smoked substance in our society. Studies conducted within the past 15 years in animals, isolated tissues, and humans indicate that marijuana smoke can injure the lungs. Habitual smoking of marijuana has been shown to be associated with chronic respiratory tract symptoms, an increased frequency of acute bronchitic episodes, extensive tracheobronchial epithelial disease, and abnormalities in the structure and function of alveolar macrophages, key cells in the lungs' immune defense system. In addition, the available evidence strongly suggests that regularly smoking marijuana may predispose to the development of cancer of the respiratory tract. "Crack" smoking has become increasingly prevalent in our society, especially among habitual smokers of marijuana. New evidence is emerging implicating smoked cocaine as a cause of acute respiratory tract symptoms, lung dysfunction, and, in some cases, serious, life-threatening acute lung injury. A strong physician message to users of marijuana, cocaine, or both concerning the harmful effects of these smoked substances on the lungs and other organs may persuade some of them, especially those with drug-related respiratory complications, to quit smoking.*

(Tashkin DP: Pulmonary complications of smoked substance abuse, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:525-530)

Humans smoke a variety of substances, including tobacco, cannabis (marijuana and hashish), alkaloidal cocaine (freebase cocaine or "crack"), phencyclidine (PCP), heroin, opium, and, most recently, methamphetamine ("ice"). The popularity of these smoked substances is due, no doubt, to the pleasure derived from the psychoactive components within the smoke, such as nicotine in tobacco and $\Delta^9$-tetrahydrocannabinol (THC) in cannabis, which also serve to reinforce the smoking habit through addiction, psychological dependence, or both.

Because the lungs are the principal organ exposed to the combustion products of smoked substances, pulmonary complications would be expected to be prominent among the health consequences of smoking. Tobacco, the most widely smoked substance in our society, has been studied extensively with regard to its adverse effects on the lungs, particularly its link to chronic obstructive pulmonary disease and lung cancer.[1,2] Much less is known about the effects on the lungs of smoking other substances, although a body of evidence is emerging implicating marijuana and crack cocaine as causes of respiratory tract disease. Because there is as yet little published information regarding the pulmonary effects of smoking other illicit substances, this article will focus mainly on our current state of knowledge concerning the respiratory complications of smoking marijuana and alkaloidal cocaine; the latter are the most widely smoked substances in our society except for tobacco, the pulmonary effects of which are already well known.

## Marijuana

Recent nationwide surveys show a continued decline in marijuana use[3,4]; nonetheless, marijuana remains one of the most widely abused substances in our society. According to a recent survey,[3] among high-school seniors about 50% were ever users of marijuana, slightly less than 40% used it within the past year, 23% used it within the past month, and 4% (6% of male students) reported using it daily. Although cannabis products are sometimes taken orally, smoking is the preferred route of administration so that the lungs are exposed first and foremost to its combustion products. These products include a number of known respiratory irritants and carcinogens[5,6] and many other compounds of which the pulmonary effects are unknown. The smoke contents of marijuana are similar in many respects to those of tobacco with the major exceptions that marijuana contains $\Delta^9$-THC and about 60 other cannabinoid compounds[5,6] whereas tobacco contains nicotine. That THC is itself a respiratory irritant is suggested by the harsh respiratory sensations elicited by the smoking of high-potency cannabis preparations and the observation that THC administered in pure form as an aerosol generally provokes cough and can cause bronchospasm in patients with asthma.[7] It is also noteworthy that most tobacco cigarettes currently in use are filter-tipped and have a relatively low tar content, but marijuana cigarettes do not contain filters and generate about twice as much tar as tobacco per unit of weight, assuming a similar smoking profile.[8] Furthermore, the techniques for smoking marijuana and tobacco differ

From the Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of California, Los Angeles, School of Medicine.
Supported by United States Public Health Service grant RO1-DA-03018 from the National Institute of Drug Abuse.
Reprint requests to Donald P. Tashkin, MD, Department of Medicine, UCLA School of Medicine, Los Angeles, CA 90024.

ABBREVIATIONS USED IN TEXT

$D_LCO$ = diffusing capacity for carbon monoxide
THC = $\Delta^9$-tetrahydrocannabinol

substantially: on the average, with marijuana the inhalation, or "puff," volume is about two-thirds larger, the depth of smoke inhalation about 40% greater, and breath holding about four times longer than those characteristic of tobacco smoking.[9] These differences in filtration and smoking technique can result in about a fourfold greater amount of tar delivered to and retained in the lungs from the smoking of marijuana than from a comparable amount of tobacco, thus potentially amplifying the harmful effects of marijuana on the lungs.

A wealth of epidemiologic, pathologic, clinical, and experimental studies have established tobacco smoking as the most important cause of lung cancer and chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.[1,2] Because of the rough similarity in smoke contents between marijuana and tobacco and the differences in filtration and smoking techniques that augment delivery of the volatile and particulate contents of marijuana smoke to the respiratory tract, there is concern that the habitual smoking of marijuana may have adverse effects on the lungs similar to those caused by tobacco smoking. The long-term respiratory consequences of tobacco smoking generally do not become clinically apparent until two or more decades after the smoking habit is initiated.[1] Because the habitual smoking of marijuana by a sizable segment of our society is a relatively recent phenomenon compared with regular tobacco smoking, sufficient time may not have transpired for the potentially harmful long-term effects of marijuana smoking on the lungs to become clinically apparent. Nonetheless, the results of studies in animals, isolated tissues, and humans during the past 15 years show that marijuana smoke has injurious effects on the lungs. I have summarized the results of these studies.

## Animal and Tissue Studies

In rats with exposure to marijuana smoke for three months in doses comparable with those used by humans, Fleischman and co-workers noted focal inflammatory changes involving the alveoli that progressed to chronic pneumonia after a year of exposure.[10,11] In tracheotomized dogs with exposure to the smoke of four marijuana cigarettes a day for 30 months, Roy and associates found severe inflammation of the peripheral airways and squamous metaplasia of the tracheal epithelium[12]; these changes were more pronounced than those noted after the same duration of daily exposure to a comparable amount of tobacco smoke. In two of ten monkeys, Heath observed fatal respiratory complications after heavy marijuana smoking for 3½ to 5½ months.[13] Huber and colleagues found that the bactericidal activity of rat alveolar macrophages was depressed by a water-soluble component of the gas phase of fresh marijuana smoke and that inactivation of pathogenic bacteria aerosolized into the lungs of rats with exposure to increasing amounts of marijuana smoke was impaired in a dose-dependent manner.[14,15] These findings suggest that marijuana smoking can impair the lungs' host defenses against infection and other noxious insults.

Several lines of experimental evidence suggest that marijuana has the potential for causing cancer of the respiratory tract. First, the smoke of marijuana contains known carcinogens, including a higher concentration of polyaromatic hydrocarbons, such as benzpyrene and benzanthracene, and a comparable amount of the volatile *N*-nitrosamines.[5] Second, in studies involving the Ames *Salmonella* microsome assay, marijuana produced mutations comparable in number with those produced by an equivalent amount of tobacco smoke condensate.[16,17] Third, marijuana smoke condensate (tar) painted on the skin of mice has shown tumorigenicity and tumor-promoting activity.[5,18] Fourth, long-term exposure of hamster lung cell cultures to marijuana smoke induced changes in the genetic material of the cell followed by irregularities in cell division that progressed to malignant transformation within three to six months of exposure; similar but less prominent abnormalities were noted during comparable exposures to tobacco.[19] Because malignant transformation also occurred in the control cultures at 12 to 24 months, the smoke of marijuana (and tobacco) appears to have accelerated rather than initiated the malignant change.

## Studies in Humans

### *Physiologic Effects*

Several studies have addressed the short- and long-term effects of marijuana smoking on lung function. While the $\Delta^9$-THC in smoked marijuana initially relaxes airway smooth muscle in both healthy persons[20,21] and stable asthmatic patients,[22] causing bronchodilation, this bronchodilator effect is relatively short-lived and diminishes with the repeated use of marijuana (tachyphylaxis).[23] In contrast to its acute bronchodilator effect, regular marijuana smoking has been shown to cause abnormal decrements in lung function, most likely due to damaging effects on airways having long-term exposure to noxious components within the smoke. After an 11-day period of abstinence, 28 healthy young men who were experienced cannabis users had mild but statistically significant airflow obstruction develop after smoking marijuana ad libitum (mean of 5.2 "joints" per day) for 6 to 8 weeks, and the decrements in lung function were correlated with the average daily amount of marijuana smoked.[23] Cessation of (or reduction in) smoking for a month led to a restoration of the baseline level of lung function, indicating that the mild impairment in airway dynamics caused by several weeks of heavy daily marijuana smoking is reversible.

Recently Tashkin and co-workers compared the lung function of heavy habitual smokers of marijuana alone (n = 144) or with tobacco (n = 137), smokers of tobacco alone (n = 70), and nonsmokers (n = 97) from the Los Angeles area.[24] The results of this comparison indicated that marijuana smoking was associated with significantly worse values for measures of large airways function, irrespective of concomitant tobacco smoking, whereas tobacco smoking adversely affected the peripheral airways and alveolated portion of the lungs, as reflected by tests of small airways function and the diffusing capacity for carbon monoxide ($D_LCO$). Repeated tests of lung function in 138 participants in the above study over three to four years continued to show adverse effects of habitual marijuana smoking on large airway function and, in addition, suggested an additive effect of marijuana and tobacco leading to further obstruction in smaller airways.[25]

Similar results were noted in an epidemiologic study of young (15- to 40-year-old) residents of Tucson, Arizona. This study showed functional evidence of airflow obstruction in male smokers of nontobacco cigarettes (mostly marijuana)

which was more prominent than that associated with tobacco smoking.[26] Moreover, the effect of smoking both types of cigarettes concurrently appeared to be additive. These findings suggest that marijuana smoking may be an important factor in young men with functional evidence of obstructive airway disease.

*Histopathologic Effects*

Fligiel and associates examined bronchial mucosal biopsy specimens obtained by fiber-optic bronchoscopy in 30 young habitual smokers of marijuana only (average of 3 to 4 joints per day), 17 smokers of both marijuana and tobacco, 15 smokers of tobacco only (average of more than 20 cigarettes per day), and 10 nonsmokers.[27] While histopathologic abnormalities in the bronchial mucosa were significantly more common and severe in each group of smokers compared with the nonsmokers, most types of mucosal abnormalities (including basal cell hyperplasia, goblet cell hyperplasia, cellular disorganization, and basement membrane thickening) were more frequent in the marijuana-only than the tobacco-only smokers. Moreover, nearly all the epithelial and basement membrane abnormalities were most commonly observed in habitual smokers of both marijuana and tobacco. These findings suggest that the daily smoking of relatively small amounts of marijuana (3 to 4 joints) has at least a comparable, if not greater, effect on tracheobronchial histopathology than the daily smoking of a much larger quantity of tobacco (more than 20 cigarettes). Further, findings show smoking both marijuana and tobacco produces additive effects on airway injury. The latter observation is consistent with earlier findings by Tennant of histopathologic abnormalities in heavy smokers of hashish or tobacco or both.[28] Whereas all hashish smokers examined by Tennant had respiratory tract symptoms and many had abnormal lung function,[28] most marijuana smokers in whom Fligiel and colleagues observed extensive microscopic changes involving the tracheobronchial epithelium were asymptomatic and had minimal or no lung function abnormality.[27] The latter findings suggest that habitual marijuana smoking causes significant, although clinically silent, airway injury at a relatively early age when symptoms and lung function are absent or relatively uncommon. The potential for the bronchoepithelial histopathology observed in marijuana smokers to progress to clinically symptomatic airways disease and lung dysfunction is as yet unknown, although such progression is certainly possible.[29-31]

*Effects on Alveolar Macrophages*

Alveolar macrophages are the most populous cells residing in the air spaces and key elements in the lungs' immune defense system. Examination of alveolar macrophages obtained by bronchoalveolar lavage from smokers of marijuana, tobacco, or both and from nonsmokers has revealed significant differences in number,[32] structure,[33] and function (M. Sherman, written communication, January 1990). Barbers and co-workers noted an increase in the number of alveolar macrophages recovered from the lungs of smokers of marijuana, tobacco, or both compared with nonsmokers.[32] Among the marijuana smokers, these increases were independent of concomitant tobacco smoking, although smoking both marijuana and tobacco appeared to have additive effects. Because the increase in the alveolar macrophage population probably represents an inflammatory response to lung injury, these findings imply an adverse effect of marijuana smoking on the lungs that is independent of and additive to that of tobacco.

On ultrastructural examination of the alveolar macrophages recovered from the lungs of the same three groups of smokers and nonsmokers, Beals and associates observed larger and more complex cytoplasmic inclusions in the macrophages of tobacco or marijuana smokers, or both, than in the nonsmokers.[33] They also observed definite ultrastructural differences between the alveolar macrophages of marijuana smokers and tobacco smokers that could indicate differences in the functional activity of these important cells. In this regard, Sherman has recently found notable differences in stimulated superoxide anion release from the alveolar macrophages of tobacco versus marijuana smokers (written communication, January 1990). Sherman has also found an impairment in microbicidal activity of alveolar macrophages from both tobacco and marijuana smokers, presumably due to a smoking-related defect in nonoxidative defense mechanisms. Together with the earlier findings of Huber and colleagues in rat alveolar macrophages,[14] these results imply that marijuana smoking, like tobacco smoking, impairs the lungs' defense against microbial invasion, thereby increasing the tendency to respiratory tract infection.

*Effects on Respiratory Tract Symptoms*

Few studies have systematically addressed the long-term effects of habitual cannabis smoking on respiratory tract symptoms and disease. The few clinical studies published in the 1970s yielded conflicting results,[34-38] probably because of small sample sizes, nonrandom sampling techniques, and a failure to control adequately for confounding factors, such as concomitant tobacco smoking. More recently, two large-scale studies carried out in Los Angeles[24] and Tucson[26] have shown a significant relationship between habitual marijuana smoking and chronic respiratory tract symptoms. The Los

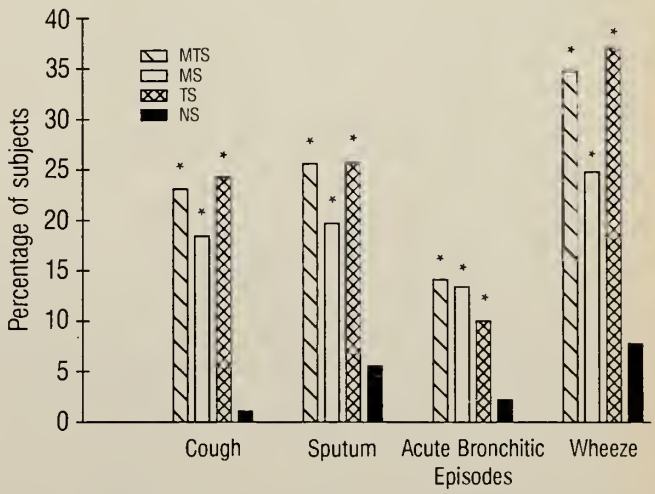



**Figure 1.**—The graph shows the proportion of smokers of both marijuana and tobacco (MTS), marijuana only (MS), tobacco only (TS), and nonsmokers (NS) with chronic respiratory tract symptoms (chronic cough, chronic sputum production, acute bronchitic episodes, and wheeze). chronic cough = cough on most days for ≥3 months out of the year for ≥2 years, chronic sputum = production of some sputum on most days for ≥3 months out of the year for ≥2 years, acute bronchitic episodes = ≥2 episodes of increased cough and sputum lasting ≥3 weeks within the past 3 years, wheeze = wheeze on ≥21 days per year, * = significantly different from NS

Angeles group studied a convenience sample of persons who habitually smoked marijuana heavily—more than 10 joints or joint-equivalents per week for more than five years—alone or with tobacco, regular smokers of tobacco only, and nonsmokers.[24] All groups consisted of men and women of roughly equivalent age (25 to 49 years) and socioeconomic status who said they did not have a history of potentially confounding factors, such as chronic respiratory tract disease, hazardous occupational exposures, smoking of cocaine or other illicit substances besides cannabis, or intravenous drug abuse. The results of this study show that those who smoke marijuana regularly have significantly more symptoms of chronic bronchitis (cough, sputum, wheeze) and a significantly greater frequency of episodes of acute bronchitis than do nonsmoking control subjects (Figure 1). No difference in the prevalence of chronic cough, sputum production, or wheeze was found between the marijuana and tobacco smokers despite the markedly different daily quantities of the two substances smoked (3 to 4 joints of marijuana versus 22 tobacco cigarettes). The similar frequency of respiratory symptoms among the two types of smokers despite the notably different numbers of cigarettes smoked per day is surprising. This finding could be due to the greater respiratory delivery of the smoke contents of marijuana compared with the smoke from an equivalent amount of tobacco as a result of differences in filtration and smoking technique, as already noted.[9]

Data from the Tucson epidemiologic study also showed a substantially higher prevalence of phlegm and wheeze in both male and female smokers (n = 100) of nontobacco cigarettes (mostly marijuana), irrespective of concomitant tobacco smoking, compared with never smokers of nontobacco cigarettes.[26] Together the data from these two studies suggest that marijuana smoking may be an important contributing factor to chronic respiratory tract symptoms in young adults.

### *Other Effects*

*Barotrauma.* Pneumomediastinum has been reported to occur after marijuana smoking.[39,40] These cases of barotrauma were most likely caused by increased intrathoracic pressure due to Valsalva maneuvers during the breath holding after deep inhalation of the smoke, leading to alveolar rupture with dissection of air along the vessels and bronchi to the mediastinum.

*Accelerated clearance of plasma theophylline.* Hydrocarbon components within the smoke of marijuana, like that of tobacco, can induce hepatic mixed oxidases to accelerate the metabolic clearance of theophylline.[41] As a consequence, the serum theophylline half-life is shortened in habitual marijuana smokers receiving theophylline. In patients treated with theophylline, therefore, it is important to inquire about marijuana- and tobacco-smoking habits because these can influence dosing requirements.

*Effects of marijuana contaminants.* Contamination of marijuana with *Aspergillus fumigatus* can cause lung disease, as illustrated by case reports of the development of allergic bronchopulmonary aspergillosis in one patient with asthma[42] and invasive *Aspergillus* species pneumonitis in two patients with impaired immunity (one with chronic granulomatous disease and the other after bone marrow transplant for chronic myelogenous leukemia) after smoking marijuana contaminated with the fungus.[43,44]

## Cocaine

The use of cocaine in the United States has increased dramatically within the past decade,[4,45] as has the prevalence of the medical complications associated with cocaine intoxication, including central nervous system reactions, catastrophic cardiovascular events, and obstetric complications.[46] According to population estimates based on the most recent national household survey,[4] 2.9% of teenagers (ages 12 through 17 years) and 12.1% of young adults (18 through 25 years) have used cocaine in the past year, whereas 1.4% of teenagers and 4% of young adults use it currently (within the past month). In recent years, smoking of alkaloidal (freebase) cocaine has replaced the nasal insufflation of cocaine hydrochloride as the most common method of use. Freebase cocaine, or crack, obtained by the alkaline extraction of the hydrochloride salt, is more suitable for smoking than cocaine hydrochloride because of its greater volatility and resistance to thermal decomposition. When freebase cocaine is smoked, usually through a water pipe or mixed with tobacco or marijuana in a cigarette, a large amount of the inhaled cocaine is absorbed by the extensive pulmonary circulation. The resultant central nervous system effects are of a similarly rapid onset and equivalent intensity to those following intravenous injection, thus contributing to the growing popularity of this method of use. At the same time, the intoxicating effects of freebase cocaine are of a relatively short duration, leading to more frequent use to maintain the euphoric high. The increasingly widespread use of smoked cocaine raises the possibility of pulmonary complications of inhaling its combustion products. Because the respiratory effects of smoking cocaine have recently been reviewed,[45] I will summarize them only briefly.

Of 19 consecutive habitual smokers of freebase cocaine admitted to a chemical dependence program, most (63%) complained of respiratory tract symptoms, including cough (58%) and shortness of breath at rest or with exercise (58%).[47] Pulmonary function tests in these smokers showed no evidence of airflow obstruction or restriction, but the $D_LCO$ was significantly reduced (less than 70% of predicted in 10 of the 19 subjects), although physiologic responses to steady-state exercise were normal.[48] Although these findings suggest that cocaine inhalation frequently induces respiratory tract symptoms and pulmonary gas exchange abnormalities, most subjects studied also gave a history of smoking tobacco and marijuana, which could have contributed to the observed respiratory abnormalities. Isolated reductions in $D_LCO$ were also reported in two patients admitted to hospital for the treatment of freebase cocaine abuse, but these abnormalities could have been accounted for by concomitant tobacco smoking and previous intravenous drug abuse with pulmonary embolism.[49] In contrast, Tashkin and associates failed to find evidence of diffusion impairment in 16 "moderate" cocaine smokers who also smoked marijuana but did not smoke tobacco or use drugs intravenously.[50] On the other hand, these authors found that the smoking of cocaine appeared to potentiate the adverse effects of tobacco on the airways, leading to substantial airflow obstruction.[47] In the same study, the following acute respiratory tract symptoms were frequently reported in temporal relation to cocaine smoking: black sputum (43%), hemoptysis (14%), and chest pain (79%) that was often pleuritic. Similar acute respiratory tract symptoms have been reported by others.[48,51] The black

sputum has been attributed to the inhalation of a tarry residue from butane torches or matches used to heat the cocaine.

Pneumothorax, pneumomediastinum, or both—the latter previously observed with marijuana smoking[39,40]—have also occurred in several patients after cocaine smoking,[52-55] most likely owing to barotrauma resulting from the extended Valsalva maneuvers associated with cocaine inhalation.

Within the past two years, the following four examples of acute diffuse lung damage have also been reported in temporal proximity to smoking cocaine:

- Noncardiogenic acute pulmonary edema accompanied by dyspnea and hypoxemia that resolved spontaneously within 72 hours[56];
- Bronchiolitis obliterans with organizing pneumonia documented on open-lung biopsy, manifested clinically by fever, nonproductive cough, dyspnea, airflow obstruction, and bilateral nodular opacities on chest x-ray films and responding to corticosteroid therapy[57];
- Recurrent pulmonary infiltrates with eosinophilia over several months, each episode after a bout of cocaine freebasing, manifested by fever, productive cough, wheezing, and dyspnea, and responding to corticosteroid therapy[58]; and
- Biopsy-proven diffuse alveolar hemorrhage (without evidence of vasculitis or the Goodpasture's syndrome) with fever, dyspnea, hemoptysis, and diffuse alveolar infiltrates.[59]

The mechanism whereby cocaine smoking might have caused acute lung injury in these cases is speculative, but suggested mechanisms have included cocaine-induced pulmonary vasoconstriction leading to anoxic cell damage, a direct toxic effect of the cocaine alkaloid on alveolar capillary endothelium, and a hypersensitivity reaction to components in the freebase smoke.

Another possible pulmonary complication of freebase cocaine is severe thermal injury to the conducting airways due to intratracheal ignition of the ether used in the freebasing process. In the one published case report, the thermal injury to the lower airways led to severe reactive airways disease and tracheal stenosis requiring surgical reconstruction.[60] Finally, cocaine smoking has been reported to cause or contribute to asthma, most likely as a result of nonspecific irritation of the airways.[61]

## REFERENCES


1. Smoking and Health: A Report of the Surgeon General, US DHEW publication No. 79-50066. US Department of Health, Education, and Welfare, Public Health Service, Office on Smoking and Health, 1979

2. The Health Consequences of Smoking: Chronic Obstructive Lung Disease. A Report of the Surgeon General, US DHHS publication No. 84-50205. US Department of Health and Human Services (DHHS), Public Health Service, Office on Smoking and Health, 1984

3. National Trends in Drug Use and Related Factors Among American High School Students and Young Adults, 1975-1986, US DHHS publication No. (ADM) 87-1535. Public Health Service, 1987

4. National Household Survey on Drug Abuse: Population Estimates 1988, US DHHS publication No. (ADM) 89-1636, Rockville, Md, National Institute on Drug Abuse, 1989

5. Hoffmann D, Brunneman DK, Gori GB, et al: On the carcinogenicity of marijuana smoke. Recent Adv Phytochem 1975; 9:63-81

6. Novotný M, Merli F, Weisler D, et al: Fractionation and capillary gas chromatographic-mass spectrometric characterization of the neutral components in marijuana and tobacco smoke condensates. J Chromatogr 1982; 238:141-150

7. Tashkin DP, Reiss S, Shapiro BJ, et al: Bronchial effects of aerosolized $\Delta^9$-tetrahydrocannabinol in healthy and asthmatic subjects. Am Rev Respir Dis 1977; 115:57-65

8. Rickert WS, Robinson JC, Rogers B: A comparison of tar, carbon monoxide and pH levels in smoke from marijuana and tobacco cigarettes. Can J Public Health 1982; 73:386-391

9. Wu TC, Tashkin DP, Djahed B, et al: Pulmonary hazards of smoking marijuana as compared with tobacco. N Engl J Med 1988; 318:347-351

10. Fleischman RW, Baker JR, Rosenkrantz H: Pulmonary pathologic changes in rats exposed to marijuana smoke for one year. Toxicol Appl Pharmacol 1979; 47:557-566

11. Fleischman RW, Hayden DW, Braude MC, et al: Chronic marijuana inhalation toxicity in rats. Toxicol Appl Pharmacol 1975; 34:467-478

12. Roy PE, Magnan-Lapointe F, Huy ND, et al: Chronic inhalation of marijuana and tobacco in dogs: Pulmonary pathology. Res Commun Chem Pathol Pharmacol 1976; 14:305-317

13. Heath RG: Testimony in Marijuana-Hashish Epidemic and Its Impact on United States Security, *In* Hearings of the Committee on the Judiciary, United States Senate. Government Printing Office, 1975, pp 50-70

14. Huber GL, Simmons GA, McCarthy CR, et al: Depressant effect of marihuana smoke on antibactericidal activity of pulmonary alveolar macrophages. Chest 1975; 68:769-773

15. Huber GL, Pochay VE, Pereira W, et al: Marijuana, tetrahydrocannabinol and pulmonary antibacterial defenses. Chest 1980; 77:403-410

16. Busch FW, Seid DA, Wei ET: Mutagenic activity of marihuana smoke condensates. Cancer Lett 1979; 6:319-324

17. Wehner FC, Van Rensburg SJ, Theil PG: Mutagenicity of marijuana and Transkei tobacco smoke condensates in the Salmonella/microsome assay. Mutat Res 1980; 77:135-142

18. Cottrell JC, Sohn SS, Vogel WH: Toxic effects of marihuana tar on mouse skin. Arch Environ Health 1973; 26:277-278

19. Leuchtenberger C, Leuchtenberger R: Cytological and cytochemical studies of the effects of fresh marihuana cigarette smoke on growth and DNA metabolism of animal and human lung cultures, *In* Braude MC, Szara S (Eds): The Pharmacology of Marijuana. New York, Raven Press, 1976

20. Vachon L, Fitzgerald MX, Solliday NH, et al: Single-dose effect of marihuana smoke: Bronchial dynamics and respiratory-center sensitivity in normal subjects. N Engl J Med 1973; 288:985-989

21. Tashkin DP, Shapiro BJ, Frank IM: Acute pulmonary physiologic effects of smoked marijuana and oral $\Delta^9$-tetrahydrocannabinol in healthy young men. N Engl J Med 1973; 289:336-341

22. Tashkin DP, Shapiro BJ, Frank IM: Acute effects of smoked marijuana and oral $\Delta^9$-tetrahydrocannabinol on specific airway conductance in asthmatic subjects. Am Rev Respir Dis 1974; 109:420-428

23. Tashkin DP, Shapiro BJ, Lee YE, et al: Subacute effects of heavy marijuana smoking on pulmonary function in healthy men. N Engl J Med 1976; 294:125-129

24. Tashkin DP, Coulson AH, Clark VA, et al: Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. Am Rev Respir Dis 1987; 135:209-216

25. Tashkin DP, Simmons MS, Clark VA, et al: Longitudinal changes in respiratory symptoms and lung function in nonsmokers, tobacco smokers, and heavy, habitual smokers of marijuana with and without tobacco, *In* Cheser G, Consroe P, Musty R (Eds): Marijuana '87: An International Research Report, Proceedings of Melbourne Symposium on Cannabis, September 1987. National Campaign Against Drug Abuse, Monograph Series No. 7. Canberra, Australia, Government Publishing Service, 1988, pp 25-30

26. Bloom JW, Kaltenborn WT, Paoletti P, et al: Respiratory effects of non-tobacco cigarettes. Br Med J [Clin Res] 1987; 295:1516-1518

27. Fligiel SEG, Beals TF, Venkat H, et al: Pulmonary pathology in marijuana smokers, *In* Cheser G, Consroe P, Musty R (Eds): Marijuana '87: An International Research Report, Proceedings of Melbourne Symposium on Cannabis, September 1987. National Campaign Against Drug Abuse, Monograph Series No. 7. Canberra, Australian Government Publishing Service, 1988, pp 31-36

28. Tennant FS Jr: Histopathologic and clinical abnormalities of the respiratory system in chronic hashish smokers. Subst Alcohol Actions Misuse 1980, 1:93-100

29. Auerbach O, Stout AP, Hammond EC, et al: Changes in bronchial epithelium in relation to cigarette smoking and in relation to lung cancer. N Engl J Med 1961; 265:253-267

30. Valentine EH: Squamous metaplasia of the bronchus. Cancer 1957; 10:272-279

31. Knudtson KP: The pathologic effects of smoking tobacco on the trachea and bronchial mucosa. Am J Clin Pathol 1960; 33:310-317

32. Barbers RG, Gong H Jr, Tashkin DP, et al: Differential examination of bronchoalveolar lavage cells in tobacco cigarette and marijuana smokers. Am Rev Respir Dis 1987; 135:1271-1275

33. Beals TF, Fliegel SEG, Stuth S, et al: Morphological alterations of alveolar macrophages from marijuana smokers (Abstr). Am Rev Respir Dis 1989; 139(pt 2):A336

34. Chopra GS: Studies on psycho-clinical aspects of long-term marihuana use in 124 cases. Int J Addict 1973; 8:1015-1026

35. Hall JAS: Testimony in Marijuana-Hashish Epidemic and Its Impact on United States Security, *In* Hearings of the Committee on the Judiciary, United States Senate. Government Printing Office, 1975, pp 147-154

36. Cruickshank EK: Physical assessment of 30 chronic cannabis users and 30 matched controls. Ann NY Acad Sci 1976; 282:162-167

37. Hernandez-Bolaños J, Swenson EW, Coggins WJ: Preservation of pulmonary function in regular, heavy, long-term marijuana smokers (Abstr). Am Rev Respir Dis 1976; 113:100(suppl)

38. Boulougouris JC, Panayiotopoulos CP, Antypas E, et al: Effects of chronic hashish use on medical status in 44 users compared with 38 controls. Ann NY Acad Sci 1976; 282:168-172

39. Miller WE, Spiekerman RE, Hepper NG: Pneumomediastinum resulting from performing Valsalva maneuvers during marijuana smoking. Chest 1972; 62:233-234

40. Mattox KL: Pneumomediastinum in heroin and marijuana users. JACEP 1976; 5:26-28

41. Jusko WJ, Schentag JJ, Clark JH, et al: Enhanced biotransformation of theophylline in marihuana and tobacco smokers. Clin Pharmacol Ther 1978; 24:406-410

42. Llamas R, Hart DR, Schneider NS: Allergic bronchopulmonary aspergillosis associated with smoking moldy marihuana. Chest 1978; 73:871-872

43. Chusid MJ, Gelfand JA, Nutter C, et al: Pulmonary aspergillosis, inhalation of contaminated marijuana smoke, chronic granulomatous disease (Letter). Ann Intern Med 1975; 82:682-683

44. Hamadeh R, Ardehali A, Locksley RM, et al: Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient. Chest 1988; 94:432-433

45. Abelson HI, Miller JD: A decade of trends in cocaine use in the household population, *In* Cocaine Use in America: Epidemiological and Clinical Perspectives. Natl Inst Drug Abuse Res Monogr Ser 1985; 61:35-49

46. Cregler LL, Mark H: Medical complications of cocaine abuse. N Engl J Med 1986; 315:1495-1500

47. Ettinger NA, Albin RJ: A review of the respiratory effects of smoking cocaine. Am J Med 1989; 87:664-668

48. Itkonen J, Schnoll S, Glassroth J: Pulmonary dysfunction in 'freebase' cocaine users. Arch Intern Med 1984; 144:2195-2197

49. Weiss RD, Goldenheim PD, Mirin SM, et al: Pulmonary dysfunction in cocaine smokers. Am J Psychiatry 1981; 138:1110-1112

50. Tashkin DP, Simmons MS, Coulson AH, et al: Respiratory effects of cocaine 'freebasing' among habitual users of marijuana with or without tobacco. Chest 1987; 92:638-644

51. Siegel RK: Cocaine smoking. J Psychoactive Drugs 1982; 14:271-359 [monograph]

52. Shesser R, Davis C, Edelstein S: Pneumomediastinum and pneumothorax after inhaling alkaloidal cocaine. Ann Emerg Med 1981; 10:213-215

53. Morris JB, Shuck JM: Pneumomediastinum in a young male cocaine user. Ann Emerg Med 1985; 14:194-196

54. Bush MN, Rubenstein R, Hoffman I, et al: Spontaneous pneumomediastinum as a consequence of cocaine use. NY State J Med 1984; 84:618-619

55. Aroesty DJ, Stanley RB Jr, Crockett DM: Pneumomediastinum and cervical emphysema from the inhalation of 'free based' cocaine: Report of three cases. Otolaryngol Head Neck Surg 1986; 94:372-374

56. Cucco RA, Yoo OH, Cregler L, et al: Nonfatal pulmonary edema after 'freebase' cocaine smoking. Am Rev Respir Dis 1987; 136:179-181

57. Patel RC, Dutta D, Schonfeld SA: Free-base cocaine use associated with bronchiolitis obliterans organizing pneumonia. Ann Intern Med 1987; 107:186-187

58. Kissner DG, Lawrence WD, Selis JE, et al: Crack lung: Pulmonary disease caused by cocaine abuse. Am Rev Respir Dis 1987; 136:1250-1252

59. Murray RJ, Albin RJ, Mergner W, et al: Diffuse alveolar hemorrhage temporally related to cocaine smoking. Chest 1988; 93:427-429

60. Taylor RF, Bernard GR: Airway complications from freebasing cocaine. Chest 1989; 95:476-477

61. Rebhun J: Association of asthma and freebase smoking. Ann Allergy 1988; 60:339-342

**Addiction Medicine**
**and the Primary Care Physician**

# Cognitive Impairments in Abstinent Alcoholics

GEORGE FEIN, PhD; LEA BACHMAN, PsyD; SARAH FISHER, PhD; *and* LINDA DAVENPORT, MS, *San Francisco*

*Impaired cognitive functioning in alcoholics is widespread during the first months of detoxification. Between half and two thirds of abstinent alcoholics exhibit cognitive impairments during this period, with residual deficits persisting for years after detoxification in some patients. The most severe deficits have been observed in visuospatial abilities, perceptual-motor integration, abstract reasoning, and new learning. The most significant predictors of cognitive dysfunction in persons recovering from alcoholism are the time elapsed since the last drink and the person's age. Surprisingly, the pattern and duration of a patient's alcohol abuse are relatively weak determinants of neuropsychological impairment during abstinence. Research investigating the hypothesis that cognitive impairments may be related to alcoholic persons resuming drinking has yielded mixed results, but a higher level of neuropsychological functioning is associated with increased rates of completing treatment programs and with greater success in the work environment after discharge from treatment. The possibility of cognitive limitations should be taken into account in planning treatment programs for alcoholism.*

(Fein G, Bachman L, Fisher S, et al: Cognitive impairments in abstinent alcoholics, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:531-537)

The deleterious effects of alcohol on cognitive functioning were reported as early as the 1880s separately by Wernicke[1] and by Korsakoff,[2] followed by Hamilton,[3] Fisher,[4] and Wechsler.[5] The studies of Fitzhugh and coworkers, introducing the clinical neuropsychological model to the study of cognitive function in alcoholism, marked the beginning of systematic research in this area.[6,7] The current literature reflects developing understanding of both the time course of the recovery of cognitive functions during abstinence and the multiple factors that may influence the presence and severity of cognitive deficits in specific patients.

Cognitive deficits in abstinent alcoholics have been identified in both men and women[8,9] and in members of different races[10] and nationalities, including Americans,[8] Canadians,[11] Danes,[12] Norwegians,[13] Scots,[14] and Swedes.[15] The deficits are widespread during the first months of abstinence, with between half and two thirds of abstinent alcoholic persons exhibiting cognitive impairments after acute detoxification.[16,17] Although the percentage of abstinent alcoholics with cognitive impairments has been reported in various study samples, there have been no large-scale epidemiologic studies establishing the prevalence of such deficits in the alcoholic population. Most studies have used convenience samples from inpatient or outpatient treatment settings; such samples are biased by the selection of patients who have sought treatment. Nonetheless, the available data illustrate the tremendous extent to which neuropsychological problems are exhibited among alcoholic patients in treatment.

Although many cognitive deficits are reversible during sustained abstinence, residual deficits persist in some patients for extended periods of time. The deficits may adversely affect patients' ability to profit from some treatment interventions and may also exert a significant effect on their lives outside of treatment. The presence and severity of cognitive impairment should inform the choice and timing of various treatment strategies. It is important to note both that not all persons with alcoholism suffer from cognitive impairments and that some deficits are unlikely to be elicited in a standard medical evaluation and may be missed unless specifically assessed.

## Cognitive Impairments as a Function of Duration of Abstinence

The most significant determinant of the presence of cognitive deficits in persons recovering from alcoholism is the time elapsed since their last drink. When this time period is controlled for, different patterns of deficits emerge for each of three time periods:

- The acute detoxification period, which lasts as long as the first two weeks of abstinence;
- The intermediate-term abstinence period, which begins after detoxification and extends through the first two months of abstinence; and
- The long-term abstinence period, which extends from two months to five years of abstinence.

The general pattern of deficits in these three time periods is displayed in Table 1.

### *Acute Detoxification (Up to 2 Weeks' Abstinence)*

Alcohol use has well-documented deleterious effects on attention, concentration, reaction time, motor coordination,

From the Department of Psychiatry, University of California, San Francisco, School of Medicine, and the Psychiatry Service, Veterans Administration Medical Center (except Ms Davenport), San Francisco.

This study was supported by the Veterans Administration General Medical Research and Rehabilitation Research and Development Programs, and from National Institute of Neurological and Communicative Disorders and Stroke grant No. RO1-NS22029-04.

Reprint requests to George Fein, PhD, VA Medical Center Box 116-R, 4150 Clement St, San Francisco, CA 94121.

TABLE 1.—*Cognitive Deficits as a Function of Duration of Abstinence*

| Cognitive Deficit | Acute Detox Period | Intermediate-term Abstinence | Long-term Abstinence |
|---|---|---|---|
| Distractibility | Yes | ... | ... |
| Mild confusion | Yes | ... | ... |
| Irritability | Yes | ... | ... |
| Attention and concentration | Yes | Yes | ... |
| Reaction time | Yes | Yes | ... |
| Verbal learning ability | Yes | Yes | ... |
| Verbal abstract reasoning | Yes | Yes | ... |
| Verbal short-term memory | Yes | Yes | ... |
| Nonverbal abstract reasoning | Yes | Yes | Yes |
| Visuospatial abilities | Yes | Yes | Yes |
| Mental flexibility | Yes | Yes | Yes |
| Nonverbal short-term memory | Yes | Yes | Yes |

Detox=detoxication

motor speed, judgment, problem-solving, learning, and short-term memory.[18-25] These effects are apparent in nonalcoholic persons as well as in alcoholics. In addition to the direct effects of alcohol on cognitive functioning, the common physiologic symptoms of detoxification, such as tremulousness, irritability, agitation, and sleep disturbance, may interfere with an alcoholic patient's test performance by reducing motivation and effort. Because these severe and pervasive impairments abate substantially with detoxification, neuropsychological assessment during this initial period is of little value. Rather, it is the residual deficits in patients following detoxification that are relevant to the diagnosis of cognitive impairment and that have implications for treatment planning.

*Intermediate-term (2 Weeks' to 2 Months') Abstinence*

After detoxification, abstinent alcoholics' overall intellectual functioning, as measured by composite IQ test scores, falls within the normal range. The composite IQ score reflects both overlearned verbal skills (crystallized intelligence) and more novel visuospatial and problem-solving skills (fluid intelligence). The crystallized intelligence of the overlearned verbal skills is intact after the detoxification period, whereas fluid intelligence skills are impaired in many patients. Because a patient's responses within a standard medical interview primarily reflect intact crystallized intelligence, the interviewing physician may get the mistaken impression that a patient's cognitive functioning is intact.

Impairments in fluid-intelligence skills of visuospatial processing and problem solving persist during the intermediate-term abstinence period in most recovering alcoholics, as evidenced by lower Performance IQ subtest scores relative to Verbal IQ subtest scores.[7,13,26,27] Recovering alcoholics also show impairments on other visuospatial and constructional tasks involving visual scanning,[28] visuomotor speed and coordination,[6,13,29,30] and disembedding figures from a complex design.[31-33] These performance deficits on complex visuospatial and constructional tasks appear to reflect impairments in higher cognitive functions of perceptual analysis and synthesis, insofar as visuosensory functioning is intact in this population.[11,34,35]

The presence, however, of motor deficits can also confound the picture of neuropsychological deficits, insofar as motor slowing, for example, can reduce performance on tests of visuomotor abilities. Tarter and Jones examined the motor functioning of abstinent alcoholics two and eight weeks after detoxification.[23] At two weeks, all patients performed significantly worse than controls on motor speed, muscle strength, and visuomotor coordination. At eight weeks, the findings were more complicated: whereas abstinent alcoholics with drinking histories of greater than ten years were still impaired on motor functioning, those who had been drinking for a shorter period performed as well as the controls. The authors concluded that motor functioning does become impaired after chronic alcohol abuse and that the shorter the period of abuse, the greater the potential for recovery with abstinence. This result implies that impaired motor functioning contributes to the pattern of neuropsychological deficits only in patients with long histories of alcohol abuse.

As indicated earlier, intermediate-term abstinent alcoholics also perform more poorly than nonalcoholic persons on tests of problem-solving and abstracting abilities. These impairments have been observed in interpreting proverbs, forming hypotheses, developing problem-solving strategies, and using feedback to monitor and correct one's responses. While some studies have failed to find deficits in verbal abstract reasoning,[7] the tests used in these studies generally involved familiar and overlearned concepts. When more challenging tests of verbal analogic reasoning are used, abstinent alcoholics do perform substantially more poorly than controls.[36,37]

One of the most sensitive tests of the impaired abstraction abilities of abstinent alcoholics is the Categories subtest of the Halstead-Reitan battery. In this test, the subject uses the pattern of examiner feedback as the basis for modifying responses to subsequent stimuli. The test requires the subject to generate alternative principles for responses, to hold in working memory the feedback to a number of responses, and to be flexible in applying alternative response patterns until he or she determines the correct one. Results from a large number of studies indicate that about 75% of intermediate-term abstinent alcoholics perform in the impaired range on this test.[13,25-27,30,38-41] The majority of this population also evidences deficits on the Tactual Performance Test, a complex spatial problem-solving task that involves inserting forms in a form board while blindfolded, and the Trail Making Test, part B, a connect-the-dots task that involves alternating between a numeric and an alphabetic series and apparently assesses cognitive flexibility.[42]

Impairments in memory and learning in abstinent alcoholics have been reported less frequently but are now receiving increasing attention. Tarter and Edwards report that learning and memory deficits were not observed when standard clinical tests were employed but were elicited by more challenging laboratory tasks.[43] Other investigators have reported short-term-memory impairments and learning deficits in both verbal and nonverbal tasks,[44-48] and studies on the reversibility of cognitive deficits reveal that scores on short-term-memory tasks improve relative to the length of abstinence.[18-20] Rather than using semantic strategies on verbal learning tasks, alcoholic patients tend to use rote learning,[49] which is a far less efficient method. Butters and Brandt have also shown retrograde memory impairments in alcoholism.[50] Overall, impairments in memory are not as conspicuous as are those in visuospatial, abstraction, and problem-solving abilities. In this regard, in a study that directly compared rates of recovery of verbal versus visuospatial

learning abilities during alcohol abstinence, visuospatial learning abilities were found to recover more slowly.[51]

The ability to learn new verbal material, which is impaired during the detoxification period, has been shown both to recover within the first two weeks of abstinence[52] and to remain impaired after a month.[20,49] This discrepancy of results may be due to the greater difficulty of the verbal learning tasks used in the studies of Weingartner and associates and Ryan.[20,49] In this regard, Weingartner and colleagues found that whereas abstinent alcoholics were equivalent to nonalcoholic controls in their ability to remember a list of words after a single presentation, with repeated trials, the alcoholic patients learned fewer additional words than did the controls.[20] Ryan also showed that abstinent alcoholics took substantially longer than controls to learn a word list,[49] but when he provided the abstinent alcoholics with mnemonic strategies for learning and remembering the words, they did as well as the control groups. These studies indicate that recovering alcoholics do show verbal learning deficits, but that these deficits are more subtle than are the deficits exhibited on visuospatial and problem-solving tasks. The results also suggest that recovering alcoholics have particular difficulty in generating effective strategies for remembering. This difficulty may be related to their problems in organizing performance on complex new tasks.

*Long-term Abstinence (Greater Than 2 Months)*

It may take several years before an abstinent alcoholic achieves full recovery of cognitive functioning in the areas of abstract reasoning, visuospatial ability, short-term memory, and mental flexibility. Moreover, a patient's age and the occurrence of interim drinking are important variables that influence the extent of the recovery of cognitive function over time. Grant and co-workers have suggested using either "intermediate-duration organic mental disorder" or "subacute organic mental disorder" to characterize the slow recovery process associated with prolonged abstinence.[32,53]

Leber and associates examined learning and memory in two groups of alcoholics abstinent for 3 and 11 weeks, respectively, and in a matched control group.[54] No differences among the three groups were observed in verbal-learning abilities; however, on a visuospatial learning task and on memory for designs, the short-term-abstinent alcoholics performed more poorly than the long-term-abstinent alcoholics, who performed more poorly than the controls. On the memory for designs task, 38% of the short-term-abstinent alcoholics were impaired compared with only 19% of the long-term-abstinent alcoholics. In a later study of visuospatial memory, Fabian and Parsons found similar results, with long-term-abstinent alcoholics performing at a level between those who were abstinent for a short term and controls.[55] Ryan and colleagues also compared short-term-abstinent alcoholics, long-term-abstinent alcoholics, and controls on a test of digit-symbol substitution.[56] They found that alcoholics performed worse than controls, with a trend, not reaching statistical significance, for long-term-abstinent alcoholics to perform better than those abstinent for a short time. Brandt and co-workers also studied prolonged-abstinent alcoholics (minimum of five years of abstinence), who they found to perform at levels indistinguishable from those of controls.[46]

Yohman and associates studied alcoholics and matched controls in a longitudinal study, with testing at 7 weeks after detoxification and again 13 months later.[57] At the initial testing, the alcoholics performed as well as the controls in learning and memory abilities but did more poorly on verbal abilities, abstracting and problem-solving skills, and perceptual-motor abilities. In their analysis of the 13-month data, they separated those alcoholics who had maintained abstinence during the 13 months from those who had resumed drinking (albeit at a reduced level). They found that the abstainers had improved in learning, memory, abstracting and problem-solving, and verbal abilities, whereas the intermittent resumers had improved only in verbal abilities. Further, even the abstainers still performed significantly worse than controls on perceptual-motor tasks 13 months after initial testing. These results show that alcoholics who resume drinking, even at a reduced level, do not achieve the same gains in cognitive function as their abstinent peers and that even abstinent alcoholics do not fully recover their cognitive abilities after 13 months.

Goldman and colleagues examined the effect of age on the recovery of visuospatial impairments in abstinent alcoholics.[58] They studied three age groups: those younger than 30 years, a group 31 to 40 years old, and those older than 40 years, and two control groups: college-aged students and army volunteers older than 40, administering 14 tests over a three-month period. At the initial testing a week after detoxification, all alcoholic groups were impaired relative to the control groups, and the oldest alcoholics were more impaired than were the two younger alcoholic groups. At three months, the two younger alcoholic groups had improved to the level of the control groups, whereas the oldest alcoholics continued to show impairment on most of the measures. Moreover, because the recovery of cognitive capacity was not found to be associated with the quantity or frequency of drinking, it was concluded that age itself was the critical variable in the failure to recover these aspects of cognitive functioning.

Finally, some cognitive changes may not be reversible even in younger abstinent alcoholics. Brandt and co-workers studied younger (mean age 42.2 years) and older (mean age 55.1 years) abstinent alcoholics after seven years of abstinence.[46] While short-term memory and psychomotor performance had returned to normal levels, deficits did persist, even in the younger group, in the learning of new verbal associations. This study suggests that some of the cognitive impairments associated with severe alcoholism may be permanent, even in relatively young alcoholic persons.

## Mediating Factors

Although the general pattern of neuropsychological impairments in abstinent alcoholics is well established, the cause of these impairments involves a mixture of biologic and environmental factors that are, as yet, poorly understood. Environmental factors include the direct or indirect neurotoxic effects of alcohol, which may be affected by the duration of alcoholism and the drinking practices—that is, binge drinking versus daily drinking; poor nutrition; a history of concomitant abuse of other drugs with central nervous system toxicity; and a history of head injury (fights, falls, and accidents). The primary biologic factors include age, preexisting neuropsychological impairments that might be related to a genetic predisposition to alcoholism, and a concomitant psychopathologic disorder. Further, structural brain changes, such as cortical atrophy, have been suggested as a possible substrate underlying cognitive deterioration. Re-

search to date has shown that a patient's age is the most potent predictor of alcohol-related cognitive dysfunction. Surprisingly, drinking practice and duration are relatively weak predictors of neuropsychological impairment in abstinent alcoholics. Most researchers have excluded from study patients with a notable abuse of other drugs, concomitant psychopathology, or with histories of substantial head trauma, so that the relative contribution of those variables to neuropsychological morbidity has not been evaluated. Similarly, although it is well documented that specific nutritional deficiencies can directly cause neuropsychological impairments, such as the syndromes described by Wernicke and by Korsakoff, nutritional status per se has not been evaluated in terms of its contribution to neuropsychological morbidity.

*Age and Cognitive Deficits in Alcoholic Patients*

A number of studies have shown that cognitive deficits are much more prevalent among older than younger alcoholics. While this might be because the aging brain is more susceptible to the toxic effects of alcohol use, studies showing cognitive deficits even among young alcoholics have led to the suggestion that alcoholism leads to "premature aging" of the brain. Ryan and Butters, for instance, showed that the performance of alcoholics on some sensitive tests of learning and memory resembled that of nonalcoholic controls approximately ten years older.[44] On the other hand, there is evidence that at least some of the alcohol-related deficits are distinguishable from those associated with normal aging—that is, that alcohol induces an "independent decrement" in cognitive decline.[59] For instance, while word-retrieval deficits and psychomotor slowing are common among the elderly, these do not typically occur in middle-aged alcoholic samples. Conversely, older alcoholics seem to have trouble with aspects of nonverbal learning that are spared among nonalcoholic elderly.[60] Whichever hypothesis accounts for the phenomenon, the overarching and clinically relevant finding in this area is that the aging process does complicate the cognitive status of alcoholics, such that they become, as they age, increasingly at risk for cognitive impairment.

From another perspective, Portnoff found that alcoholics who began drinking at a mean age of 14 years showed more severe cognitive impairments than did alcoholics who started drinking at a mean age of 23 years, even though the number of years of heavy drinking did not differ between the two groups.[61] These results suggest that alcoholics who began drinking in their teens may be particularly vulnerable to the neuropsychological morbidity of alcohol abuse.

*Biologic Trait Variables*

There is overwhelming evidence that genetic factors predispose children of alcoholics towards alcoholism.[11,34,62-64] Children of alcoholics also exhibit a distinctive pattern on electroencephalograms and cortical evoked-potential testing,[65-68] consistent with a genetically determined trait manifesting itself in altered brain function. Tarter and colleagues reported that although their overall IQs were indistinguishable from the offspring of nonalcoholics, the sons of alcoholics performed worse on tests of educational achievement.[69,70] Schaeffer and associates also found evidence of neuropsychological impairment in relatives of alcoholics compared with those of nonalcoholic persons.[71] Additionally, many alcoholics were hyperactive as children,[72-75] and hyperactivity is associated with attentional and learning difficulties. De Obaldia and Parsons found that alcoholics with evidence of childhood hyperactivity performed worse on neuropsychological testing than did alcoholics without evidence of childhood hyperactivity.[76] Although the results regarding neuropsychological and achievement deficits in children of alcoholics may reflect a mixture of biologic and environmental factors, they are consistent with the conjecture that genetic factors may partially mediate the neuropsychological morbidity of alcohol abuse.

*Structural Brain Changes of Alcoholism*

Structural brain changes of alcoholism were first observed on postmortem examinations[77] and using pneumoencephalography.[78] With the introduction of computed tomography and magnetic resonance imaging, these observations have been replicated by numerous investigators.[32,79-85] Widened sulci have been found consistently in patients of all ages with chronic alcoholism. This widening is particularly apparent in the frontal and the frontoparietotemporal areas.[32,79] Jernigan and colleagues noted that the degree of sulcal widening seen in 40- to 60-year-old alcoholic patients resembled that seen in 70- to 90-year-old controls.[84] Ventricular dilation also occurs in alcoholics but is not as common as cortical atrophy and tends to occur predominantly in older alcoholics.[84,86,87] Jernigan and co-workers found a significant correlation between lifetime alcohol consumption and sulcal and ventricular enlargement.[84] Serial computed tomographic scans suggest that cerebral atrophy reverses over time as abstinence continues,[48,88] with more complete recovery of cortical volume in younger than in older alcoholics.[88]

Studies exploring the relationship between cognitive performance and structural brain changes have generally yielded disappointing results. Although several studies of alcoholism have reported significant correlations between intellectual impairment and cerebral atrophy,[89-91] when age and IQ are controlled for, these associations usually diminish or disappear.[86] The relationship between cerebral atrophy and cognitive impairment in alcoholism may be similar to that seen in aging and dementia, where the presence of even severe cerebral atrophy, by itself, is not diagnostic of cognitive impairments.

*Neuropsychological Impairments in Alcoholic Women*

Most research on cognitive function in recovering alcoholics has used samples of male veterans in inpatient or outpatient alcohol treatment programs. The relative vulnerability of women to cognitive deficits associated with chronic alcohol abuse has received only limited study, with inconsistent results to date. While most studies report the same deficits in alcoholic women as in alcoholic men, such as impairments in abstraction and in visuospatial abilities,[92] some studies have reported gender-related differences.[54] Some studies that compare cognitive functioning of alcoholic women and men show better performance among the women in visuospatial-paired associates[93] and in both verbal and visual short-term memory[92]; however, other studies find additional deficits in women, such as in verbal abstraction ability,[94] or report the same pattern of deficits in women as in men, but with greater severity among women.[95,96] Acker, in a study of 33 female and 72 male alcoholics matched by age, education, and estimated premorbid intelligence, found that women showed cognitive impairments comparable to those of men in pattern and severity, despite shorter drinking histo-

ries and a lower average daily consumption.[95] When drinking histories were equated either by subject-matching or by statistical control, women showed more severe deficits than men in short-term memory for verbal and visual material and in psychomotor speed. Although there are some inconsistencies among these studies, possibly as a function of methodologic or sample differences, it is safe to conclude that female alcoholics, like their male counterparts, are at risk for substantial cognitive deficits.

*Alcoholism Duration and Consumption Characteristics*

While the duration of alcoholism has been found to have a small positive correlation with the severity of some cognitive impairments, this effect becomes statistically insignificant when the effects of patient age are controlled for.[41,97,98] Variables such as the amount consumed per drinking occasions and the distinction among bout, binge, and daily drinkers have also been evaluated as predictors of the severity of neuropsychological deficits but have been found to explain little cognitive test performance variance.[98,99] These studies suggest that the drinking history and pattern are not of primary importance in mediating the presence or severity of cognitive impairments in abstinent alcoholics.

The prevalence of cognitive deficits in alcoholic patients has led some investigators to the study of the cognitive status of social drinkers. Most studies have examined the relationship between cognitive performance and aspects of drinking practice such as average amount of alcohol consumed per occasion, frequency of drinking occasions, and total alcohol consumed per time period. In a thorough review of this literature, Parsons concludes that, although relationships have occasionally been reported between drinking variables and performance on cognitive-perceptual tests, there are no stable and reproducible results.[100] While heavy alcohol consumption may put persons at risk for cognitive impairments, more research is needed to establish this as a fact. Clearly, the risks are not as high for social drinkers as for persons whose alcohol consumption has been more extensive.

## Implications of Cognitive Impairments for Treatment Planning

Tumarkin and associates first proposed that brain damage may be related to a poor prognosis for rehabilitation in alcoholic patients.[101] In support of this hypothesis, higher levels of neuropsychological functioning have been shown to be associated with increased rates of the completion of inpatient treatment[102] and with attendance at outpatient treatment groups.[14] In addition, the neuropsychological status was also found to be a statistically significant predictor of employment success nine months after discharge from treatment.[103-106]

In a discussion of the implications of cognitive impairments for the treatment of alcoholism, McCrady and Smith describe the timing of treatment interventions as often being inappropriate to the capabilities of a cognitively impaired patient.[105] They note that

> [In] the earliest phases of inpatient rehabilitation, patients are asked to learn new information, interact verbally in individual and group therapy, and to make difficult connections between events, actions, and feelings which they have perceived as unconnected (a difficult abstraction task). . . . All of this occurs while verbal deficits, retention deficits, and abstraction/problem-solving are most impaired! We expect all patients to learn and progress through treatment at approximately the same rate, whether or not they are able to do so.[105(p147)]

After discharge from inpatient programs, the patient's tasks become even more complex. He or she must deal with family members, neighbors, co-workers, and occupational issues, all in the context of possible drinking stimuli and situations. Unfortunately, even though problem-solving and abstraction abilities may still be impaired during this period, most treatment plans call for reduced treatment contacts.

Sensitivity to the possibility of cognitive impairments in abstinent alcoholics is essential to informed treatment planning. Patients with deficits in their ability to learn new information are at a disadvantage in intensive treatment programs. They may be erroneously labeled as "unmotivated" or "not ready to stop drinking," rather than as "impaired," and their higher rates of treatment dropout may result from frustration over the inability to function effectively in a program that makes unrealistic cognitive demands. We agree with McCrady and Smith's suggestion that a different approach be taken with the neuropsychologically impaired patient: Early treatment should focus on enforced abstinence and should be primarily supportive, without making major demands on patients to learn new material or to think about their experience in an analytic fashion. As cognitive functioning improves, patients may begin to participate in the more educational and insight-oriented aspects of rehabilitation.

We note that the Alcoholics Anonymous program is appropriate to the cognitive limitations of newly abstinent alcoholic persons. The focus in Alcoholics Anonymous is on maintaining abstinence from alcohol within the context of acceptance and support. New initiates are told to come to as many meetings as possible ("90 meetings in 90 days"), without an expectation that they become fully indoctrinated into the culture of the program ("fake it until you make it"). Indeed, during the initial period, the emphasis is on behavioral change rather than on understanding or a change of attitude.

Because most alcoholics do show some cognitive deficits, at least during early abstinence, it is important for all health care workers involved in treatment to be alert to the possibility of cognitive impairment. Some treatment settings[106] have begun to screen all incoming patients with a brief assessment of some cognitive functions and to use results of this screening as the basis for expectations of the patient's ability to make use of various aspects of the treatment setting. More research is needed into the relationship between cognitive deficits and the ability to profit from different kinds of interventions. In the absence of such knowledge, we recommend minimizing cognitive demands on patients early in abstinence.

Finally, while cognitive status does predict the ability to benefit from early treatment efforts and to maintain employment, intact cognition is not associated with continuing abstinence.[103,104] Thus, while the cognitive status may be highly relevant to the success of early intervention in alcoholism, it may not be predictive of long-term recovery. Therefore, it must be remembered that even those alcoholics with normal cognitive functioning during abstinence nevertheless continue to be at risk for resuming drinking practices.

### REFERENCES

1. Wernicke C: Lehrbuch der Gehirnkrankheiten fur Aerzte und Studirende. Theodor Fisher, Kassel U. Berlin 1881; 2:229-242

2. Korsakoff S: Disturbance of psychic activity in alcoholic paralysis. Vestn Klin Psichiat Neurol 1887; 4:1-102

3. Hamilton CL: Alcohol and the mind. Illinois Med J 1906; 9:39-46

4. Fisher JT: Mental defects following the use of alcohol. S Calif Practitioner 1910; 25:569-572

5. Wechsler D: The effect of alcohol on mental activity. Q J Stud Alcohol 1941; 2:479-485

6. Fitzhugh LC, Fitzhugh KB, Reitan RM: Adaptive abilities and intellectual functioning in hospitalized alcoholics. Q J Stud Alcohol 1960; 21:414-423

7. Fitzhugh LC, Fitzhugh KB, Reitan RM: Adaptive abilities and intellectual functioning in hospitalized alcoholics: Further considerations. Q J Stud Alcohol 1965; 26:402-411

8. Parsons OA, Farr S: The neuropsychology of alcohol and drug use, chap 10, *In* Filskov S, Boll T (Eds): Handbook of Clinical Neuropsychology. New York, Wiley, 1981, pp 320-365

9. Hochla NN, Fabian M, Parsons OA: Brain age quotients in recently detoxified alcoholic, recovered alcoholic, and non-alcoholic women. J Clin Psychol 1982; 38:207-212

10. Hill S, Mikhale M: Computerized transaxial tomographic and neuropsychological evaluations in chronic alcoholics and heroin abusers. Am J Psychiatry 1979; 136:598-602

11. Wilkinson DA, Carlen PL: Neuropsychological and neurological assessment of alcoholism: Discrimination between groups of alcoholics. J Stud Alcohol 1980; 41:129-139

12. Lee K, Jensen E, Bech P: Neuropsychological and computerized tomographic evaluation of young alcoholics. Br J Psychiatry 1982; 41:282-285

13. Løberg T: Alcohol misuse and neuropsychological deficits in men. J Stud Alcohol 1980; 41:119-128

14. Guthrie A, Elliott WA: The nature and reversibility of cerebral impairment in alcoholism: Treatment implications. J Stud Alcohol 1980; 41:147-155

15. Berglund M, Leijonquist H, Hörlén M: Prognostic significance and reversibility of cerebral dysfunction in alcoholics. J Stud Alcohol 1977; 38:1761-1770

16. Miller WR, Saucedo CF: Assessment of neuropsychological impairment and brain damage in problem drinkers, chap 11, *In* Golden W, Moses JA, Coffman JA, et al (Eds): Clinical Neuropsychology: Interface with Neurological and Psychiatric Disorders. New York, Grune & Stratton, 1983, pp 141-196

17. Parsons OA: Alcoholics' neuropsychological impairment: Current findings and conclusions. Ann Behav Med 1986; 8:13-19

18. Allen RP, Faillace LA, Reynolds DM: Recovery of memory functioning in alcoholics following prolonged alcohol intoxication. J Nerv Ment Dis 1971; 153:417-423

19. Allen RP, Faillace LA, Wagman A: Recovery time for alcoholics after prolonged alcohol intoxication. Johns Hopkins Med J 1971; 128:158-164

20. Weingartner H, Faillace LA, Markley HG: Verbal information retention in alcoholics. Q J Stud Alcohol 1971; 32:293-303

21. Page RD, Linden JD: 'Reversible' organic brain syndrome in alcoholics during abstinence—A psychometric evaluation. Q J Stud Alcohol 1974; 35:98-107

22. Clarke J, Haughton H: A study of intellectual impairment and recovery rates in heavy drinkers in Ireland. Br J Psychiatry 1975; 12:178-184

23. Tarter RE, Jones B: Motor impairment in chronic alcoholics. Dis Nerv Syst 1971; 32:632-636

24. Farmer RH: Functional changes during early weeks of abstinence, measured by the Bender-Gestalt. Q J Stud Alcohol 1973; 34:786-795

25. Long JA, McLachlan JFC: Abstract reasoning and perceptual-motor efficiency in alcoholics—Impairment and reversibility. Q J Stud Alcohol 1974; 35:1220-1229

26. Løberg T, Miller WR: Personality, cognitive, and neuropsychological correlates of harmful alcohol consumption: A cross-national comparison of clinical samples. Ann NY Acad Sci 1986; 472:75-97

27. Kleinknecht RA, Goldstein SG: Neuropsychological deficits associated with alcoholism: A review and discussion. Q J Stud Alcohol 1972; 33:999-1019

28. Bertera JH, Parsons OA: Impaired visual search in alcoholics. Alcoholism (NY) 1978; 2:9-14

29. Goldstein G, Shelly CH: Field dependence and cognitive, perceptual and motor skills in alcoholics: A factor analytic study. Q J Stud Alcohol 1971; 32:29-40

30. Parsons OA, Leber WR: The relationship between cognitive dysfunction and brain damage in alcoholics: Causal, interactive, or epiphenomenal? Alcoholism (NY) 1981; 5:326-343

31. Bergman H, Agren G: Cognitive style and intellectual performance in relation to the progress of alcoholism. Q J Stud Alcohol 1974; 35:1242-1255

32. Grant I: Alcohol and the brain: Neuropsychological correlates. J Consult Clin Psychol 1987; 55:310-324

33. Sugerman A, Schneider D: Cognitive styles in alcoholism, chap 11, *In* Tarter R, Sugerman A (Eds): Alcoholism: Interdisciplinary Approaches to an Enduring Problem. Reading, Mass, Addison-Wesley, 1976, pp 395-433

34. Ryan C, Butters N: Cognitive deficits in alcoholics, chap 12, *In* Kissin B, Begleiter H (Eds): The Pathogenesis of Alcoholism—Vol 7, Biological Factors. New York, Plenum Press, 1983, pp 485-538

35. Tarter RE: Psychological deficit in chronic alcoholics: A review. Int J Addict 1975; 10:327-368

36. Jonsson C, Croholm B, Izikowitz S: Intellectual changes in alcoholics: Psychometric studies on mental sequels of prolonged intensive abuse of alcohol. Q J Stud Alcohol 1962; 23:221-242

37. Yohman JR, Parsons OA: Verbal reasoning deficits in alcoholics. J Nerv Ment Dis 1987; 175:219-223

38. Grant I, Reed R: Neuropsychology of alcohol and drug abuse, chap 11, *In* Alterman AI (Ed): Substance Abuse and Psychopathology. New York, Plenum Press, 1985, pp 298-341

39. Jones B, Parsons OA: Impaired abstracting ability in chronic alcoholics. Arch Gen Psychiatry 1971; 24:71-75

40. Jones B, Parsons OA: Specific vs generalized deficits of abstracting ability in chronic alcoholics. Arch Gen Psychiatry 1972; 26:380-384

41. Svanum S, Schladenhauffen J: Lifetime and recent alcohol consumption among male alcoholics: Neuropsychological implications. J Nerv Ment Dis 1986; 174:214-220

42. Chelune GJ, Parker JB: Neuropsychological deficits associated with chronic alcohol abuse. Clin Psychol Rev 1981; 1:181-195

43. Tarter RE, Edwards KL: Neuropsychology of alcoholism, chap 8, *In* Tarter RE, Van Thiel DH (Eds): Alcohol and the Brain: Chronic Effects. New York, Plenum Press, 1985, pp 217-244

44. Ryan C, Butters N: Learning and memory impairments in young and old alcoholics: Evidence for the premature-aging hypothesis. Alcoholism (NY) 1980; 4:288-293

45. Becker JT, Butters N, Hermann A, et al: A comparison of the effects of long-term alcohol abuse and aging on the performance of verbal and nonverbal divided attention tasks. Alcoholism (NY) 1983; 7:213-219

46. Brandt J, Butters N, Ryan C, et al: Cognitive loss and recovery in long-term alcohol abusers. Arch Gen Psychiatry 1983; 40:435-442

47. Cutting J: Specific psychological deficits in alcoholism. Br J Psychiatry 1978; 133:119-122

48. Ron MA, Acker W, Lishman WA: Morphological abnormalities in the brains of chronic alcoholics: A clinical, psychological, and computerized axial tomographic study. Acta Psychiatr Scand 1980; 62:41-46

49. Ryan C: Learning and memory deficits in alcoholics. J Stud Alcohol 1980; 41:437-447

50. Butters N, Brandt J: The continuity hypothesis: The relationship of long-term alcoholism to the Wernicke-Korsakoff syndrome, chap 13, *In* Galanter M (Ed): Recent Developments in Alcoholism—Vol 3. New York, Plenum Press, 1985, pp 207-226

51. Ellenberg L, Rosenbaum G, Goldman MS, et al: Recoverability of psychological functioning following alcohol abuse: Lateralization effects. J Consult Clin Psychol 1980; 48:503-510

52. Sharp JR, Rosenbaum G, Goldman MS, et al: Recoverability of psychological functioning following alcohol abuse: Acquisition of meaningful synonyms. J Consult Clin Psychol 1977; 45:1023-1028

53. Grant I, Adams KM, Reed R: Intermediate-duration (subacute) organic mental disorder of alcoholism, chap 3, *In* Grant I (Ed): Neuropsychiatric Correlates of Alcoholism. Washington, DC, American Psychiatric Press, 1986, pp 38-59

54. Leber WR, Jenkins RL, Parsons OA: Recovery of visual-spatial learning and memory in chronic alcoholics. J Clin Psychol 1981; 37:192-197

55. Fabian MS, Parsons OA: Differential improvement of cognitive functions in recovering alcoholic women. J Abnorm Psychol 1983; 92:87-95

56. Ryan C, DiDario B, Butters N, et al: The relationship between abstinence and recovery of function in male alcoholics. J Clin Neuropsychol 1980; 2:125-134

57. Yohman JR, Parsons OA, Leber WR: Lack of recovery in male alcoholics' neuropsychological performance one year after treatment. Alcoholism (NY) 1985; 9:114-117

58. Goldman MS, Williams DL, Klisz DK: Recoverability of psychological functioning following alcohol abuse: Prolonged visual-spatial dysfunction in older alcoholics. J Consult Clin Psychol 1983; 51:370-378

59. Grant I, Adams KM, Reed R: Aging, abstinence, and medical risk factors in the prediction of neuropsychologic deficit among long-term alcoholics. Arch Gen Psychiatry 1984; 41:710-718

60. Butters N: Cognitive defects of long-term alcoholics: Ecological validity and premature aging. Read at the 11th Annual Meeting of the International Neuropsychological Society, Mexico City, February 3, 1983

61. Portnoff L: Halstead-Reitan impairment in chronic alcoholics as a function of age of drinking onset. Clin Neuropsychol 1982; 4:115-119

62. Cotton NS: The familial incidence of alcoholism: A review. J Stud Alcohol 1979; 40:89-116

63. Cadoret RJ, Cain CA, Grove WM: Development of alcoholism in adoptees raised apart from alcoholic biologic relatives. Arch Gen Psychiatry 1980; 37:561-563

64. Cloninger CR, Bohman M, Sigvardsson S: Inheritance of alcoholic abuse: Cross-fostering analysis of adopted men. Arch Gen Psychiatry 1981; 38:861-868

65. Goodwin D, Schulsinger R, Hermansen L, et al: Alcoholism and the hyperactive child syndrome. J Nerv Ment Dis 1975; 160:349-353

66. Cantwell D: Psychiatric illness in the families of hyperactive children. Arch Gen Psychiatry 1972; 27:414-417

67. Elmasian R, Neville H, Woods D, et al: Event-related brain potentials are different in individuals at high and low risk for developing alcoholism. Proc Natl Acad Sci USA 1982; 79:7900-7903

68. Begleiter H, Porjesz B, Bihari B, et al: Event-related brain potentials in boys at risk for alcoholism. Science 1984; 225:1493-1496

69. Tarter RE, Hegedus A, Goldstein G, et al: Adolescent sons of alcoholics: Neuropsychological and personality characteristics. Alcoholism (NY) 1984; 8:216-222

70. Hedegus AM, Alterman AI, Tarter RE: Learning achievement in sons of alcoholics. Alcoholism (NY) 1984; 8:330-333

71. Schaeffer KW, Parsons OA, Yohman JR: Neuropsychological differences between male familial and nonfamilial alcoholics and nonalcoholics. Alcoholism (NY) 1984; 8:347-351

72. Gomberg E: The young male alcoholic: A pilot study. J Stud Alcohol 1982; 43:683-700

73. Jones MC: Personality correlates and antecedents of drinking patterns in adult males. J Consult Clin Psychol 1968; 32:2-12

74. Tarter RE, McBride H, Buonpane N, et al: Differentiation of alcoholics according to childhood history of minimal brain dysfunction, family history and drinking pattern. Arch Gen Psychiatry 1977; 34:761-768

75. Wood D, Reimherr F, Wender P, et al: Diagnosis and treatment of minimal brain dysfunction in adults. Arch Gen Psychiatry 1976; 33:1453-1460

76. De Obaldia R, Parsons OA: Relationship of neuropsychological performance

related to primary alcoholism and self-reported symptoms of childhood minimal brain dysfunction. J Stud Alcohol 1984; 45:386-392

77. Adams RD, Victor M, Mancall EL: Central pontine myelinolysis: A hitherto undescribed disease occurring in alcoholic and malnourished patients. Arch Neurol Psychiatry 1959; 81:154-172

78. Courville CB: Effects of Alcohol on the Nervous System of Man. Los Angeles, San Lucas Press, 1966

79. Begleiter H, Porjesz B, Tenner M: Neuroradiological and neurophysiological evidence of brain deficits in chronic alcoholics. Acta Psychiatr Scand [Suppl] 1980; Suppl 286:3-13

80. Bergman H, Borg S, Hindmarsh T, et al: Computed tomography of the brain and neuropsychological assessment of alcoholic patients. Adv Exp Med Biol 1980; 126:771-786

81. Bergman H, Borg S, Hindmarsh T, et al: Computed tomography of the brain and neuropsychological assessment of male alcoholic patients and a random sample from the general male population. Acta Psychiatr Scand [Suppl] 1980; Suppl 286:47-56

82. Cala LA, Mastaglia FL: Computerized tomography in chronic alcoholics. Alcoholism (NY) 1981; 5:283-294

83. Fox JH, Ramsey RG, Huckman MS, et al: Cerebral ventricular enlargement: Chronic alcoholics examined by computerized tomography. JAMA 1976; 236:365-368

84. Jernigan TL, Pfefferbaum A, Zatz L: Computed tomography correlates in alcoholism, chap 2, *In* Grant I (Ed): Neuropsychiatric Correlates of Alcoholism. Washington, DC, American Psychiatric Press, 1986, pp 21-36

85. Pfefferbaum A, Rosenbloom M, Crusan K, et al: Brain CT changes in alcoholics: Effects of age and alcohol consumption. Alcoholism (NY) 1988; 12:81-87

86. Ron MA: The alcoholic brain: CT scan and psychological findings. Psychol Med [Monogr Suppl] 1983; Suppl 3:1-33

87. Wilkinson DA: Neuroradiologic investigations of alcoholism, chap 7, *In* Tarter RE, Van Thiel DH (Eds): Alcohol and the Brain: Chronic Effects. New York, Plenum Press, 1985, pp 183-216

88. Carlen PL, Wortzman G, Holgate RC, et al: Reversible cerebral atrophy in recently abstinent chronic alcoholics measured by computed tomography scan. Science 1978; 200:1076-1078

89. Cala LA, Jones B, Mastaglia FL, et al: Brain atrophy and intellectual impairment in heavy drinkers: A clinical, psychometric and computerized tomography study. Aust NZ J Med 1978; 8:147-153

90. Cala LA, Jones B, Wiley B, et al: A computerized axial tomography (CAT) study of alcohol induced cerebral atrophy. Acta Psychiatr Scand [Suppl] 1980; Suppl 286:31-40

91. Carlen PL, Wilkinson DA: Alcoholic brain damage and reversible deficits. Acta Psychiatr Scand 1980; 62:103-118

92. Sparadeo FR, Zwick W, Butters N: Cognitive functioning of alcoholic females: An exploratory study. Drug Alcohol Depend 1983; 12:143-150

93. Fabian MS, Parsons OA, Shelton MD: Effects of gender and alcoholism on verbal and visual-spatial learning. J Nerv Ment Dis 1984; 172:16-20

94. Hatcher EM, Jones MK, Jones BM: Cognitive deficits in alcoholic women. Alcoholism (NY) 1977; 1:371-377

95. Acker C: Neuropsychological deficits in alcoholics: The relative contributions of gender and drinking history. Br J Addict 1986; 81:395-403

96. Bergman H: Brain dysfunction related to alcoholism: Some results from the KARTAD project, chap 2, *In* Parsons OA, Butters N, Nathan P (Eds): Neuropsychology of Alcoholism. New York, Guilford Press, 1986, pp 21-45

97. Adams KM, Grant I: Failure of non-linear models of drinking history variables to predict neuropsychological performance in alcoholics. Am J Psychiatry 1984; 141:663-667

98. Eckardt MJ, Parker ES, Noble EP, et al: Relationship between neuropsychological performance and alcohol consumption in alcoholics. Biol Psychiat 1978; 13:551-565

99. Tarbox AR, Connors GJ, McLaughlin EJ: Effects of drinking pattern on neuropsychological performance among alcohol misusers. J Stud Alcohol 1986; 47:176-179

100. Parsons OA: Cognitive functioning in sober social drinkers: A review and critique. J Stud Alcohol 1986; 47:101-114

101. Tumarkin G, Wilson J, Snyder G: Cerebral atrophy due to alcoholism in young adults. US Armed Forces Med J 1955; 6:67-74

102. O'Leary MR, Donovan DM, Chaney EF, et al: Cognitive impairment and treatment outcome with alcoholics: Preliminary findings. J Clin Psychol 1979; 40:397-398

103. Walker K, Sanchez-Craig M, Bornet A: Teaching coping skills to chronic alcoholics in a coeducational halfway house: II. Assessment of outcome and identification of outcome predictors. Br J Addict 1982; 77:185-196

104. Walker RD, Donovan D, Kivlahan D, et al: Length of stay, neuropsychological performance, and aftercare: Influences on alcohol treatment outcome. J Consult Clin Psychol 1983; 51:900-911

105. McCrady BS, Smith DE: Implications of cognitive impairment for the treatment of alcoholism. Alcoholism (NY) 1986; 10:145-149

106. Meek PS, Clark HW, Solana VL: Neurocognitive impairment: The unrecognized component of dual diagnosis in substance abuse treatment. J Psychoactive Drugs 1989; 21:153-160

**Addiction Medicine**
**and the Primary Care Physician**

# Primary Care for AIDS and Chemical Dependence

LORI D. KARAN, MD, *Richmond, Virginia*

*Primary care clinicians are acquiring an increasingly important role in preventing, diagnosing, and treating both chemical dependence and human immunodeficiency virus (HIV) illness. Towards this end they need to know the epidemiology of HIV infection in chemically dependent persons and methods of educating persons at high risk for these problems. It is critical that physicians screen for alcohol and drug addiction. Health care providers should understand the risks and benefits of HIV antibody testing and include in their practices the basic components of counseling before and after testing and informed consent. Both HIV illness and addiction are chronic diseases with long-term health implications. A knowledge of patient characteristics, intensity of treatments, and treatment modalities is important in making recommendations for individualized therapy. Combining service delivery is a future challenge necessitated by today's joint epidemics of the acquired immunodeficiency syndrome and chemical dependence.*

(Karan LD: Primary care for AIDS and chemical dependence, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:538-542)

Chemically dependent persons are at high risk for acquiring the human immunodeficiency virus (HIV). Between 1985 and 1987, HIV seropositivity in persons enrolled in drug treatment programs ranged between 0% and 65%. It is estimated by cross-sectional and cohort studies that this rate may increase between 0% and 14% yearly. If between 5% and 33% of intravenous drug abusers in the United States are infected with HIV, and assuming that 90% of all intravenous drug users live in urban areas and that 15% of the urban drug users are in drug treatment programs, then it can be calculated that between 61,000 and 398,000 intravenous drug users in the United States are currently infected.[1] There is a potential for the rapid spread of HIV in regions of the country where rates are currently low. In contrast, in Manhattan, New York City, the virus entered the drug-using population in the mid-1970s, spread rapidly in 1979 through 1983, and the seroprevalence rate stabilized from 1984 to 1987. This stabilization is attributed to the combination of various factors including the rates of new infection, seronegative persons just beginning injecting drugs, seropositive persons stopping drug injection, and increasing conscious risk reduction.[2]

The seroprevalence of HIV infection among intravenous drug users in the United States is geographically variable. The highest seroprevalence rates are found in New York City, and this rate decreases in the Northeast with increasing distance from this location. In the Northeast, HIV seroprevalence ranges between 10% and 65%, and in other areas these rates have been as follows: Puerto Rico, 45% to 59%; Baltimore, 29%; Atlanta, 10%; Detroit, 7% to 13%; San Francisco, 7% to 13%; and Los Angeles, 5%.[1]

Higher rates of HIV infection are found in African Americans and Hispanics. Although African Americans represent 12% and Hispanics 6% of the population in the United States, they account for 27% and 15%, respectively, of all people with the acquired immunodeficiency syndrome (AIDS). According to studies of households, African Americans are twice as likely as whites to have used drugs intravenously (Press Office of the National Institute on Drug Abuse, "NIDA Capsules," 1989). Also, their higher rate of HIV infection may be related in part to their injection behavior and social setting. Schoenbaum and co-workers in 1989 reported that the presence of HIV antibody was associated with a low income, a more recent year of last drug injection, the number of injections per month, and the percentage of drug injections that took place in "shooting galleries" or in which needles and paraphernalia were shared among other persons.[3]

A study of heterosexual intravenous drug users in public methadone treatment programs in San Francisco in 1986 and 1987 before the advent of "crack" showed that persons who injected cocaine had a higher risk of being HIV-seropositive.[4] The increased risk of HIV infection in cocaine users is probably associated with their more frequent daily injections due to the short half-life and highly addictive nature of this drug. In addition, a subgroup of cocaine users have increased libido and may exchange sex for drugs.[5] Persons with alcoholism and a history of intravenous drug abuse have HIV-seroprevalence rates similar to other injection drug users in their area. In metropolitan New York and northern New Jersey, alcoholics who did not have a history of intravenous drug use had a relatively low rate (4.5%) of HIV-seropositivity. This 1 in 20 rate, however, is still significant in light of the disinhibiting effects of alcohol on risky sexual behaviors and its possible immunosuppressive activity.[6]

The number of women and children with HIV infection is rapidly increasing. As of January 2, 1989, of the 81,418 cases of adult AIDS reported to the Centers for Disease Control, 6,983 (8%) were women, of whom 3,622 (52%) were

From the Inpatient Services, Division of Substance Abuse Medicine, Departments of Medicine and Psychiatry, Medical College of Virginia Hospitals, Virginia Commonwealth University, Richmond, Virginia.

Reprint requests to Lori D. Karan, MD, Division of Substance Abuse, Medical College of Virginia Hospitals, 1200 E Broad St, Rm 1148, Richmond, VA 23219.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

female intravenous drug users and 1,257 (18%) had sex partners with histories of intravenous drug use. Infected African-American and Hispanic women were more likely than white women to have had histories of intravenous drug use or of sex with intravenous drug users. Among children with AIDS, 78% are presumed to have acquired the HIV infection perinatally from their mothers.[7] These trends are worrisome in that intravenous drug use is the conduit of HIV infection to both the heterosexual and pediatric populations.

Human immunodeficiency virus type 1 infection may have a larger impact on the morbidity and mortality of intravenous drug users than accounted for by previous AIDS surveillance techniques.[8] In a study by Stoneburner and associates, a dramatic increase in non-AIDS narcotics-related deaths occurred in New York City residents between 1978 and 1986 due to pneumonia, endocarditis, sepsis, tuberculosis, meningitis, neoplasms, chronic renal failure, and gastrointestinal and cardiovascular disorders.[9] The revised Centers for Disease Control definition of AIDS takes into account only some of these conditions.

## Prevention

Although we continue to gain knowledge of retroviruses and to develop medications to prolong the life of those infected with HIV, it is not expected that there will be either a vaccine or a cure in the near future. Our only hope of stemming the AIDS epidemic is through prevention by education and subsequent behavioral risk reduction.

Persons addicted to drugs are an unorganized and leaderless group who are driven underground by their illegal activities, poor self-image, and low sense of self-worth. They are not readily reached by traditional methods of communication and health service delivery. In addition, governmental "get tough" approaches to drug addiction tend to further isolate and alienate this population.

Collaborative efforts between street-outreach public health workers and intravenous drug users are a more positive and effective approach to this problem.[10] More than 50 cities in the United States now have active AIDS outreach prevention programs for intravenous drug users. Recovering addicts, ethnographers, and health educators present themselves on the streets and in shooting galleries where drug users congregate. Not only do they provide persons who are at high risk of acquiring HIV infection personalized risk assessment and education, but they often supply them with written instructional material, bleach, or condoms to encourage safer methods of drug injection and sexual behavior. In addition, they may analytically observe the activities of persons in this subculture to determine the factors that increase the rates of HIV transmission and the effectiveness of their behavioral interventions. Drug users have frequently responded by "sponsoring" these persons, providing them access to other drug users and ensuring their safety. In Minneapolis and in New York, health workers are joining with intravenous drug users to organize formal AIDS risk-reduction groups.

Watters and Newmeyer pioneered street outreach in San Francisco in 1986.[11] Because it was illegal to provide clean needles and syringes, bleach was promoted as an effective, quick, inexpensive, safe, and convenient method for disinfecting drug use equipment. Boiling "works" in water is another safe method of sterilization. Initially there was a concern that teaching safer drug use would promote drug abuse. Data now show, however, that these programs have increased and not decreased the demand for drug treatment. It is not the needle and syringe or bleach but the personalized contact that is important. Successful outreach workers also link their clients to other medical and social services.

Primary care physicians frequently provide care to chemically dependent persons and their sexual partners who are at risk of HIV infection. Several studies have found a 25% to 40% prevalence of addiction (excluding nicotine addiction) in patients admitted to hospitals.[12,13] Primary care physicians need to provide culturally sensitive counseling and education to their patients. Health information, literature, and videotapes can be obtained from a variety of resources including state and local medical societies and AIDS organizations such as the National AIDS Information Clearinghouse.

In 1985 Selwyn and colleagues studied intravenous drug users at Rikers Island Prison in New York City.[14] Using assessment questionnaires before and after structured informational sessions, they were the first to show that intravenous drug users could acquire new knowledge from educational interventions.[14] Getting persons to change their behaviors, however, is more complex and requires additional motivational and skill-building tactics. Small graduated changes over time need to be progressively reinforced. Future data from the National Institute on Drug Abuse's National AIDS Outreach Demonstration Research Projects initiated in 1987 and now in operation at 63 sites throughout the United States should give us additional insights into reaching and effecting behavioral change in such special target populations as drug users who are not in treatment, the sexual partners of drug users, prostitutes, and homeless youths.

## Screening

To initiate treatment, it is important that primary care physicians be able to diagnose both chemical dependence and HIV infection. The history, physical examination, and laboratory information are used to corroborate diagnoses of substance intoxication, withdrawal, or chemical dependence. Addiction can be defined as a chronic disorder of compulsive use that results in physical, social, and psychological manifestations and continuous use despite adverse consequences. Therefore, in addition to asking patients questions about their quantity of consumption and frequency of use of alcohol and other psychoactive drugs, questions concerning family history of addiction, tolerance, withdrawal symptoms, and the adverse consequences associated with substance abuse should be posed. These topics should include family relationships, social network and support, occupational history, criminal record, physical trauma, associated illnesses or infections, nutrition, and psychological distress. Anxiety, when issues of attempts at and loss of control are discussed, is a diagnostic "red flag" more dependent on the tone than the content of the interview. A nonjudgmental atmosphere within the context of a therapeutic setting is needed so that drug users do not alter their stories for the purposes of social desirability and acceptance.

Supplemental evidence of substance abuse can be obtained during a patient's physical and laboratory examina-

tions. Signs associated with alcohol use include tremor, diaphoresis, facial flushing, ataxia, rosacea, telangiectasias, Dupuytren's contractures, palmar erythema, an enlarged liver, ascites, and peripheral neuropathy. Stigmata of psychoactive drug use include localized nasal erythema or perforation, track marks, skin abscesses, phlebitis, pupillary changes, goose flesh (piloerection), rhinorrhea, myalgias, abdominal cramping, and inflamed conjunctivae (marijuana). In addition, laboratory values including an increased mean corpuscular volume, alterations in the number of platelets, abnormal values on liver function tests, decreased albumin levels, and increased uric acid concentrations may be associated with alcoholism. Indicators of poor nutrition and false-positive rapid plasma reagin tests frequently occur in drug users. The use of a breath analyzer to determine alcohol levels and urine toxicology to screen for drug addiction may be indicated.

Data obtained from a history, physical examination, and laboratory tests are also important in corroborating the diagnosis of HIV illness. The American Society on Alcoholism and other Drug Dependencies has taken a position against routine mandatory testing for HIV antibody. It is felt that the decision to recommend HIV testing should be individualized and take into account the potential benefits and disadvantages of this information.[15] There is no research that can predict behavioral outcome given only the knowledge of a positive or negative antibody test result. Thorough and compassionate counseling before and after the test coupled with informed consent is essential to the testing process. An outline of the benefits and disadvantages of HIV antibody testing is given in Table 1. Some valid reasons for considering the test include wanting to know whether or not a person is infected or infectious and concern that some specific behavioral (marriage or pregnancy), diagnostic, or therapeutic changes are necessary. Some reasons for questioning the wisdom of immediate HIV testing include pressure from a family member, "significant other," or agency or institution to share test results, a patient with a history of adverse reactions under stress, and indications that a positive test result may precipitate a patient's abrupt termination from medical or chemical dependence treatment. Legislation to protect against discrimination and safeguard confidentiality would greatly benefit persons who are in need of HIV testing.

The timing of HIV antibody testing in chemically dependent persons must occur after withdrawal is stabilized and is preferable when a patient is emotionally stable. Pretest counseling should include determining a person's motivation for testing, the person's risk factors, or current illness(es), or both, the nature and purpose of HIV testing, what positive and negative test results do and do not mean, the benefits and risks of the test, and the limits of confidentiality. Also, the patient should be helped to anticipate possible reactions to the test results and to achieve closure on the testing decision, and a care plan if testing is or is not done should be discussed. Informed consent is part of the process of pretest counseling. Post-test counseling should reiterate the content of pretest counseling. Reinforcing safer sexual and drug behavior and assessing the need for retesting is important for those persons with a negative test result. Arranging for medical follow-up, social services, and support groups is indicated for persons who test HIV antibody-positive. It is the role of primary care physicians to counsel and educate their HIV antibody-positive patients about HIV illness and infectivity while helping them to tell others who are at risk from HIV exposure. The duty to warn identifiable others who are at risk when a patient does not wish to tell these persons remains an ethical decision with undetermined legal implications.

In a recent article by Perry and co-workers discussing

TABLE 1.—*Benefits and Disadvantages of Testing for Human Immunodeficiency Virus (HIV) Antibody Status*

| *Benefits* | *Disadvantages* |
|---|---|
| **Medical—To guide therapeutic interventions** | **Chemical Dependency** |
| *Diagnostic significance* | Potential for addictions relapse, an abrupt termination from treatment, or both |
| Symptomatic patients are at high risk for accompanying disease | **Psychiatric** |
| Certain AIDS-equivalent syndromes, presumptive diagnoses of opportunistic infections, and other infections now require positive HIV antibody tests to qualify as AIDS level diagnoses | Potential for depression, stress, anxiety, and suicide |
| *Treatment* | **Social*** |
| Opportunistic infections may be treated differently in an HIV-positive patient | Ostracism from family, friends, and neighbors (too often, HIV-positive persons lack the support of others when they most need it) |
| Tuberculosis, syphilis, hepatitis δ-infections, subacute bacterial endocarditis, and other infections may require more close observation and aggressive treatment in an HIV-positive patient | **Economic*** |
| *Intervention* | Potential for job loss |
| Treatments are becoming available to prevent or delay AIDS or ARC from developing in seropositive persons | Potential for disqualification from health and life insurance |
| Immunosuppressive therapy for another disease may not be indicated for an HIV-positive patient | **Public Health** |
| *Prevention* | HIV-negative persons may use this as a rationale to not change their high-risk behavior |
| An HIV-positive woman may consider abortion early in pregnancy or may defer pregnancy | An HIV-positive person may be irresponsible or vindictive (or both) in infecting others |
| If vaccine becomes available, this may protect persons from becoming infected with the virus | |
| **Psychological** | |
| If HIV-negative: relief of anxiety | |
| If HIV-positive: able to make meaningful life assessments, changes, and plans in the context of limited time | |
| **Economic** | |
| Gain third-party payments, such as Medicaid or disability benefits | |
| Plan personal affairs, draw up a will, and so forth | |
| **Public Health** | |
| An HIV-negative person may increase measures to protect self | |
| An HIV-positive person may increase measures to protect others (and self) | |

AIDS = acquired immunodeficiency syndrome. ARC = AIDS-related complex

*Social and economic disadvantages may become magnified if confidentiality is not assured and antidiscriminatory policies and laws are not in place.

depression in persons who test HIV-positive,[16] 244 men and 57 women who were physically asymptomatic but perceived to be at risk for HIV infection volunteered for free confidential testing with counseling in a private office in New York City. They were given the Beck Depression Inventory two weeks before notification of their HIV-antibody test result and both one and two months afterwards. The rates of suicidal ideation on item 9 of the Beck Depression Inventory were 28.6% at entry and 27.1% and 16.3%, respectively, at the one- and two-month follow-up assessments among the 49 seropositive subjects. This index was also measured among 252 seronegative subjects. Suicidal ideation was found in 30.6%, 17.1%, and 15.9% of seronegative persons at these respective times. Among the persons who had suicidal wishes or intent at any assessment, average modified Beck Depression Inventory scores (mean, 17.1) suggested a clinical depression. It is of concern that even in the context of confidential testing with extensive pretest and post-test counseling, more than 15% of both groups of self-selected volunteers had persistent suicidal ideation after notification of their test result. This subpopulation of physically asymptomatic persons at risk for HIV infection may also have an increased risk of psychiatric morbidity.

## Treatment

Infection with the human immunodeficiency virus and chemical dependence are both chronic diseases that are characterized by exacerbations and remissions. A framework of providing a spectrum of services for long-term health care is needed when conceptualizing the treatment of either or both illnesses.

Prescribing therapy for patients at any given time during their illness requires a knowledge of the patients' characteristics, potential treatment modalities, and the intensity of available treatments. With respect to patient characteristics, the severity of addiction can be qualitatively assessed by knowing the quantity of drug(s) used, the route(s) of administration, the pattern of their use, and related social, psychological, and physical adverse consequences. The acuteness of HIV infection is determined by the severity of associated opportunistic infections, malignant lesions, dementia, and other illnesses. Surrogate markers are currently being evaluated for their prognostic implications. T4 lymphocyte counts, p24 antigenemia, and levels of $\beta_2$-microglobulin are the markers most widely employed today. Knowledge of a patient's support system is important in assessing treatment needs in both instances.

Pharmacologic and nonpharmacologic therapies are available for both illnesses. The chemical dependence field today is being challenged by the need to combine its abstinence philosophy with pharmacologic treatments such as methadone hydrochloride for opiate addiction.[17] This is especially important because there have not yet been developed proven effective pharmacologic treatments for alcoholism and cocaine addiction. The armament for treating HIV illness includes not only established and experimental antimicrobial agents for the treatment of opportunistic infections and remedies for other symptoms and complications of HIV illness, but also drugs that interfere with viral attachment, action, and replication, and medications that aid in immune reconstitution. Nonpharmacologic therapies for addiction include individual counseling, group therapy, support groups, family therapy, Alcoholics and Narcotics Anonymous meetings, cognitive and behavioral therapies, psychotherapy, psychodrama, spirituality, stress management, relaxation, and the like. Many of these techniques also help to improve the quality of life of those with HIV-spectrum diseases.

Research has not yet quantitated the benefits of nonpharmacologic therapy. In the addictions field, helping patients link their use of drugs to adverse consequences and achieve a self-diagnosis of chemical dependence is central to therapy. Thereafter, offering the widest array of therapeutic services to each client and seeing through a process of trial and error which method best works for each person is optimum. Studies that match similar patients to various treatment methods and compare outcomes are now being done.

The intensity of treatment is characterized by the amount or lack of structure involved in a given modality and the specified time commitment and frequency of therapy. Admission to hospital and outpatient visits are the two ways of providing care most familiar to physicians. Addictions treatment often takes place in nonhospital residential facilities and halfway houses and is indicated for those who are medically stable but need structure and support away from their home environment. Intensive outpatient counseling is being provided with increased frequency. Home visits, nursing home, and hospice care are greatly needed by persons with AIDS. Health facilities more proximate to high prevalence areas of drug addiction and HIV infection could be more frequently provided by health teams in medical vans and better situated clinics.

Both the avoidance of illicit drug use and retention in treatment are important goals in treating chemical dependence. Although there has not yet been a controlled study showing that persons who continue to use drugs have a more rapid progression of HIV infection,[18] there are reasons that drug abusers are at an increased risk for acquiring, transmitting, and having a rapid advancement of HIV illness to AIDS and death. Using alcohol and other drugs may disinhibit unsafe needle and sexual practices, increasing exposure of the user and others to the virus. Alcohol and other drugs may alter the immune state so that they diminish natural killer-cell activity,[19-22] and they may cause defects in other humoral mechanisms[23]; they are also associated with increased carcinogenesis and mutagenesis.[24] Drug abusers have increased rates of infections other than HIV,[8,25] including sexually transmitted diseases, infections associated with intravenously injecting adulterants (such as endocarditis, hepatitis), and those associated with poor living conditions (pneumonia, tuberculosis). Persons addicted to drugs are often in poor health from a lack of self-care, poor nutrition, and a stressful life-style. Drug abusers, including those persons with psychiatric comorbidity, frequently delay seeking medical care and have diminished compliance with medical regimens. The rejection of timely medical care is becoming increasingly detrimental to these persons as zidovudine (AZT) and other effective therapies for HIV illnesses are becoming available.

Addictions treatment is important in improving the quality of life of those persons infected with HIV. When AIDS patients at Baker Place in San Francisco were asked why they wanted chemical dependence treatment and sobriety, they gave the following responses: "to complete something in my life," "to find a purpose in my life," "to plan the things I want to do with the rest of my life," "to make peace with my family," and "to get my life together (with respect to wills, custody of children, and the disposition of one's own

body)."[26] Drugs short-circuit the process of social interaction, and addictions treatment is necessary to reestablish healthier interpersonal relationships. With social supports restored, society benefits as these patients incur a lesser cost of care in part by diminishing their length of stay in institutions. Moreover, chemical dependence treatment is helpful in improving the quality of patients' lives by increasing their self-esteem, improving their sense of well-being, and helping them attain spirituality.

As the number of infected intravenous drug users continues to increase, the responsibilities of drug abuse treatment programs in providing HIV-related medical services and linking their clients to additional community resources are also expanding. Such medical care could include both the treatment of acute illness and chemoprophylaxis for tuberculosis, zidovudine, and aerosolized pentamidine isethionate therapy for *Pneumocystis carinii* pneumonia prophylaxis. To provide these services, however, funding, reimbursement, and staffing for drug treatment programs need to be correspondingly enhanced.[27] The capacity of drug treatment programs also needs to be expanded to enable greater public access to treatment rather than interminably long waiting lists.

Primary care physicians also will need to accept an increasing amount of responsibility in providing services for chemically dependent or HIV-infected persons, as the sheer number of these patients is overcoming the modest number of persons with specialty training in either addiction or infectious diseases. Primary care physicians need to develop the knowledge and the clinical skills necessary to attain accurate sexual and drug abuse histories, provide counseling on safer sex and drug use practices, furnish counseling before and after HIV antibody testing, help in evaluating chemical dependence and HIV-related symptoms, aid HIV-positive women with decisions surrounding pregnancy, assist patients with decisions about the availability of treatment options and aggressiveness of treatment, and link persons to available community resources. It is the challenge of primary care physicians to prevent, diagnose, and treat the immediate problems and risks associated with drug addiction, slow the potential genocide of AIDS, and increase the quality of life for those afflicted with these illnesses.

## REFERENCES


1. Hahn RA, Onorato IM, Jones S, et al: Prevalence of HIV infection among intravenous drug users in the United States. JAMA 1989; 261:2677-2684

2. DesJarlais DC, Friedman SR, Novick DM, et al: HIV-1 infection among intravenous drug users in Manhattan, New York City, from 1977 through 1987. JAMA 1989; 261:1008-1012

3. Schoenbaum EE, Harter D, Selwyn PA, et al: Risk factors for human immunodeficiency virus infection in intravenous drug users. N Engl J Med 1989; 321:874-879

4. Chaisson RE, Bacchetti P, Osmond D, et al: Cocaine use and HIV infection in intravenous drug users in San Francisco. JAMA 1989; 261:561-565

5. Weiss S: Links between cocaine and retroviral infection. JAMA 1989; 261:607-608

6. Schleifer SJ, Keller SE, Lombardo JM, et al: HIV-1 antibody reactivity in inner-city alcoholics (Letter). JAMA 1989; 262:2680-2681

7. Centers for Disease Control: Update: Acquired Immunodeficiency Syndrome—United States, 1981-1988. MMWR 1989; 38:229-236

8. Selwyn PA, Hartel D, Wasserman W, et al: Impact of the AIDS epidemic on morbidity and mortality among intravenous drug users in a New York City methadone maintenance program. Am J Public Health 1989; 79:1358-1362

9. Stoneburner RL, DesJarlais DC, Benezra D, et al: A larger spectrum of severe HIV-1-related disease in intravenous drug users. Science 1988; 242:916-919

10. DesJarlais DC, Friedman SR: Shooting galleries and AIDS: Infection probabilities and 'tough' policies. Am J Public Health 1990; 80:142-144

11. Watters JK, Newmeyer JA, Feldman HW, et al: Street-Based AIDS Prevention for Intravenous Drug Users in San Francisco—Prospects, Options, and Obstacles. Community Epidemiology Work Group Proceedings, Vol 11. Rockville, Md, US Dept of Health and Human Services, 1986, pp 37-43

12. Moore RD, Bone LR, Geller G, et al: Prevalence, detection, and treatment of alcoholism in hospitalized patients. JAMA 1989; 261:403-407

13. Soderstrom CA, Trifillis AL, Shankar BS, et al: Marijuana and alcohol use among 1023 trauma patients. Arch Surg 1988; 123:733-737

14. Selwyn PA, Cox CP, Reiner C, et al: Knowledge About AIDS and High-Risk Behavior Among Intravenous Drug Abusers in New York City. Presented at the Annual Meeting of the American Public Health Association, Washington, DC, 1985

15. Official AMSAODD Position on Treatment—Adopted November 1985 in Guidelines for Facilities Treating Chemically Dependent Patients at Risks for AIDS or Infected by HIV Virus. New York, American Medical Society on Alcoholism and Other Drug Dependencies, 1988

16. Perry S, Jacobsberg L, Fishman B: Suicidal ideation and HIV testing. JAMA 1990; 263:679-682

17. Nathan JA, Karan LD: Substance abuse treatment modalities in the age of HIV spectrum disease. J Psychoactive Drugs 1989; 21:423-429

18. Kaslow RA, Blackwelder WC, Ostrow DG, et al: No evidence for a role of alcohol or other psychoactive drugs in accelerating immunodeficiency in HIV-1 positive individuals: A report from the multicenter AIDS cohort study. JAMA 1989; 261:3424-3429

19. Donahoe FM, Falek A: Neuroimmunomodulation by opiates and other drugs of abuse: Relationship to HIV infection and AIDS, *In* Bridges TP, Mirsky AF, Goodwin RK (Eds): Psychological, Neuropsychiatric and Substance Abuse Aspects of AIDS. Adv Biochem Psychopharmacol 1988; 44:145-158

20. Friedman H, Klein T, Specter S, et al: Drugs of abuse and virus susceptibility, *In* Bridges TP, Mirsky AF, Goodwin RK (Eds): Psychological, Neuropsychiatric and Substance Abuse Aspects of AIDS. Adv Biochem Psychopharmacol 1988; 44:125-137

21. Klein TW, Newton CA, Friedman H: Suppression of human and mouse lymphocyte proliferation by cocaine, *In* Bridges TP, Mirsky AF, Goodwin FK (Eds): Psychological, Neuropsychiatric and Substance Abuse Aspects of AIDS. Adv Biochem Psychopharmacol 1988; 44:139-143

22. MacGregor RR: Alcohol and immune defense. JAMA 1986; 256:1474-1479

23. Tubaro E, Auico U, Santiangeli C, et al: Morphine and methadone impact on human phagocytic physiology. Int J Immunopharmacol 1985; 7:865-874

24. Osterloh J, Goldfield D: Butyl nitrite transformation in vitro, chemical nitrosation reactions, and mutagenesis. J Anal Toxicol 1984; 8:164-169

25. Mondanaro J: Strategies for AIDS prevention: Motivating health behavior in drug dependent women. J Psychoactive Drugs 1987; 19:143-149

26. Ferguson J: AIDS Psychopathology: A Multiple Diagnosis Program. Presented at AIDS and Chemical Dependency: Multidisciplinary Approaches to Clinical Skills and Public Policy, San Francisco, November 1987

27. Selwyn PA, Feingold AR, Iezza A, et al: Primary care for patients with human immunodeficiency virus (HIV) infection in a methadone maintenance treatment program. Ann Intern Med 1989; 110:761-763

**Addiction Medicine**
**and the Primary Care Physician**

# Addiction in Adolescents

MARTHA A. MORRISON, MD, *Atlanta*

*Some symptoms seen in adolescents with the disease of chemical dependence are similar to those seen in adults. Because of their age, lack of personality development, dependent family role, immaturity, and acting out of age-related behavioral tendencies, however, symptoms specific to this population occur. These may become exacerbated and telescope—intensify and shorten—the progression of the disease. A plan to solve the problem of adolescent chemical dependence must focus on education, demonstration, cooperation, prevention, intervention, habilitation, treatment, and recovery. The phenomenon of denial in a chemically dependent adolescent yields a more complex delusional system that dictates age-specific intervention approaches. Habilitation is necessary for successful adolescent treatment and recovery because what is needed is an initial process of learning, not relearning or rehabilitation. If specific adolescent issues are addressed through comprehensive, multimodality treatment approaches, then treatment and recovery outcomes for chemically dependent adolescents and their families are substantially improved. Primary care physicians must be alert to the possibility of drug use in their young patients and aware of treatment options.*

(Morrison MA: Addiction in adolescents, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:543-546)

Adolescence is a confusing and complex period in life, a time of questioning, exploring, and risk taking. Drug experimentation is becoming an increasingly prevalent part of an adolescent's rite of passage. Young people are responding en masse to the alluring promise of today's chemical culture, which seems to promise quick relief and instant gratification, popularity, and an attractive peer group, not to mention sexual prowess and financial success. All of these offerings, which represent primary adolescent issues and desires, are enhanced further through television, one of the primary reference sources for the adolescent population.

## Progression of Drug Use in Adolescents

Research indicates several reasons for adolescent drug experimentation: drugs are often readily available; they provide a quick, easy, and cheap way to feel good. They offer a means to gain acceptance in peer relationships and to modify unpleasant feelings, reduce disturbing emotions, alleviate depression, reduce tension, and aid in coping with life pressures. Most adolescents, however, probably ingest drugs to feel powerful, to be "cool," and to be in with a group.[1]

The effects of drug abuse include difficulty with concentration, mood, coordination, and judgment. Drugs may cause paranoia, hallucinations, and agitation. Problems with memory, impaired attention span, and delayed maturation may lead to school dysfunction.[1]

The leading causes of death among young Americans between the ages of 15 and 24 stem from violent events—homicides, suicides, and accidents. A significant number of these can be attributed to using alcohol and drugs.[2]

In 1986, 65% of high school seniors reported using alcohol on a monthly basis, 30% used cigarettes, 23% marijuana, and 6% cocaine. Most high school seniors have tried illicit drugs.[3] Overall, 61% of seniors in 1985 admitted to such use, and 40% admitted using an illicit drug other than marijuana. According to MacDonald, 54% of high school seniors have tried marijuana at some time, 17% have tried cocaine, and 26% have tried amphetamines.[2]

Adolescents who use one drug are likely to use another. They usually begin with legal drugs—alcohol or tobacco—progress to marijuana, and may eventually go on to other drugs or combinations of drugs. About half of adolescents who try marijuana will eventually progress to more potent drugs. Conversely, the use of drugs such as cocaine or heroin is unusual in young people who have not previously used alcohol, tobacco, or marijuana.[4] Alcohol and tobacco, particularly, and sometimes marijuana are thus known as "gateway" drugs; their use greatly increases the probability of later use of other substances.

With certain variations, adolescents biologically and genetically predisposed to chemical dependence follow a fairly well-marked path to addiction when exposed to mood-altering substances. They spend time using and abusing substances before exhibiting early, then advanced, symptoms of addiction.[5] This journey is considerably more rapid in adolescents than in adults[1,5-7] and appears to be related to age, sex, ethnic origin, and drug of choice. This increased progression and rapidity of the disease process and increased morbidity and mortality of juvenile or adolescent chemical dependence appear similar to other adolescent medical illness, such as juvenile diabetes mellitus or juvenile rheumatoid arthritis.

Many factors differentiate adult and adolescent chemical dependence. Polydrug use is much more prevalent among teens. The teens themselves are often unaware of the quantities and types of drugs they have been using, which makes

From the Young Adult Services, Anchor Hospital, and the Anchor Recovery Team and Young Adult Services, Talbott Recovery System, Atlanta.
Reprint requests to Martha A. Morrison, MD, Medical Director, Young Adult Services, Anchor Hospital, 5454 Yorktowne Dr, Atlanta, GA 30349.

medical assessment and a differentiation between chemical abuse and addiction more difficult. The reasons for chemical use in adolescents are also different from those usually seen in adults. Adolescent drug use is more internally motivated rather than due to outside stressors or external motivation. Most adolescents use drugs to feel better or to cover up unpleasant feelings, to increase their confidence and self-esteem, and often just to experience the "high" the drugs give them.

## Recognition and Intervention

The progression of the disease makes early recognition and intervention all the more crucial. The more entrenched denial—that is, delusional—system in adolescents is another factor that affects the identification and recognition of symptoms. Most adolescents do not experience the more dramatic withdrawal symptoms seen in adults or the dramatic long-term consequences of adult drug use, such as loss of job, home, spouse, and family. Adolescents are usually protected by a larger system of enablers—teachers, peers, and, most profoundly, parents—all making it difficult to admit that a problem exists.

Keeping in mind the need to address all of the specific clinical needs of this age group, it is also imperative to recognize that the disease of addiction manifests itself in all realms of an adolescent's life—physical, psychological, sociologic, spiritual—just as it does with their adult counterparts.[6] The manifestations, however, are simply emotionally, behaviorally, attitudinally, and chronologically more developmentally specific.

Although the American Medical Association recognized alcoholism as a disease in 1954, it has only been in the past decade that health care professionals have begun to realize that the disease of chemical dependence manifests itself in the adolescent population because most adolescents did not have physical dependence or well-defined withdrawal symptoms, nor did they exhibit the physiologic deterioration so commonly seen in adult alcoholics and addicts. The open drug culture of the 1960s and early 1970s did much to shed light on the extent of the drug problem in the adolescent population.[2] As emergency departments became flooded with adolescent drug overdoses and complications, it became apparent that some teenagers were more than socially involved. Many of these adolescents showed the same social deterioration that was being seen in adult addiction or alcoholism—they dropped out of school, out of family, and, all too frequently, out of life.[8]

### *Early Addiction*

Addiction may begin with experimental use of substances at a young age. The average age of first use is between 11 and 12 years.[9] Many teens begin use as a result of peer pressure. More recently there has been an increasing number of adolescents whose first encounter with mood-altering substances occurs within the home. Parents are the most powerful role models children have. Adolescents are likely to emulate their parents' drinking or drug use patterns. More teens in treatment today are reporting that their first use of alcohol or other drugs occurred with parental supervision. This experience translates to a belief that the use and abuse of chemicals are permissible. Coupled with the emotional immaturity of the adolescent, the potential danger of this message is obvious. Use in the early stages of addiction becomes more regular, with the teen putting more mental and physical energy into obtaining and ingesting drugs and alcohol. As use begins to increase and become more regular, teens begin to depend on chemicals as a coping mechanism. They report increased feelings of self-assurance, security, and belonging.

### *Intermediate Addiction*

Intermediate addiction is characterized by the accumulation of adverse consequences in an adolescent's life. As the disease begins to progress, teens experience a shift in priorities, a change in attitude, and an increase in denial. They begin to have problems in school, at work, and at home, with family and friends, legally, emotionally, and physically. The phenomenon of denial becomes increasingly entrenched, precluding the realization of the connection between adverse consequences and chemical use. Denial does not allow adolescents to see themselves or their situation as it really is, and thus permits them to believe the lie of control over chemical use.

### *Advanced Addiction*

As a chemically dependent adolescent's use continues, the disease escalates to advanced addiction. Because of an abundance of enablers and the ability to con, hide, and lie about drug use, it is not uncommon for parents not to recognize that their teen is even involved in drugs until the disease has progressed to an advanced level. During advanced addiction, consequences compound, becoming more noticeable externally, while the emotional pain, low self-esteem, and loneliness increase internally. The adolescent perpetuates a cycle of compulsive use, negative physical, emotional, and social consequences, negative feelings about self, and increased chemical use to escape these feelings. Unless intervention takes place, a chemically dependent adolescent's disease will continue to progress to imprisonment, institutionalization, or premature death.

## Prevention and Treatment

Adolescents appear more vulnerable or susceptible to the addiction process. Young people are at risk of exposure to chemicals in today's society, and those who are genetically or biologically predisposed to addiction will clearly manifest this chronic, progressive, potentially fatal disease if untreated.[5,10,11] Chemical abuse and progression are preventable, however, and chemical dependence when present is treatable.

One of the most important ways to solve the problem of substance abuse is to change perceptions and attitudes about chemical abuse and dependence. Education begins this process. Facts about alcohol and drug abuse can be taught so that substance abuse can be perceived as an unacceptable means of coping with everyday life. Accurate information regarding addictive disease allows an understanding that precludes moral and ethical stigmas often associated with alcoholism and drug addiction. True understanding is then demonstrated by actions. Demonstration, therefore, simply implies responsible and effective role modeling. Furthermore, the cooperation of school and community programs with churches, youth services, and parental organizations assists adolescents in achieving full emotional and social growth and improving interpersonal interactions.

The prevention of chemical dependence may be the result of education, demonstration, and cooperation. The best

teaching is, of course, by example and can occur most effectively in the home environment early in a teenager's life. A distinct change in attitude, as well as in the way Americans perceive substance use, abuse, and addiction, is crucial for the primary prevention of this disease. Learning about the problem and altering the way the problem is perceived can impart the knowledge necessary to prevent it.

Because of denial and a false sense of invulnerability, adolescents tend to have an angry, rebellious, and resistant attitude towards changing their life-style and getting help. They less frequently ask for or openly accept help than do adults.[1] Treatment is commonly precipitated by legal, parental, school, or peer intervention in which a teen is faced with alternatives such as jail, expulsion from school, or leaving home versus receiving help. The phenomenon of denial dictates the need for intervention that allows the adolescent the opportunity for motivation. Intervention implies caring about someone enough to risk that person's anger and hostility temporarily as a result of the confrontation and intervention process.

Habilitation can then be seen as necessary for adolescents because what is required is an initial process of learning, not relearning or rehabilitation. Habilitation is generally defined as providing conditions that allow an adolescent to mature emotionally while acquiring nonchemical coping skills. Both peers and healthy adults are necessary to this process—in the treatment facility and in the home, school, and community. Improving interpersonal interactions, an increased sense of responsibility, honest and open communication abilities, self-respect, self-confidence, and an increased sense of security must be obtained and developed during this process.

External controls and structure are essential for adolescents to develop internal controls. It is normal for adolescents to test limits and to manipulate the external structure that is provided. It is imperative that the parent or health professional enforce these limits consistently, thereby promoting discipline and a sense of responsibility. It is necessary for parents, authority figures, and health professionals to set good examples because adolescents are extremely impressionable. What they see and hear becomes a part of them. Teenagers simply mirror adult attitudes and behavior. It is important to remember that scars are easier to prevent than to erase.

The effective chemical dependence treatment program for an adolescent must not be concerned only with the biogenetic or physiologic aspect of the disease but must also address and compensate for the emotional problems and needs that underlie the initial experimentation and usage. In addition, because of the arrest of emotional developmental due to substantial drug use, coping and developmental skills must be learned for the first time—that is, habilitation versus rehabilitation.

For successful treatment and recovery to occur, certain factors and differences must be understood and adequately addressed. Some of these factors include a treatment approach to chemical dependence as a psychosocial, biogenetic disease, recognizing the more entrenched denial and accelerated progression of the disease in this age group, the prevalence of dual diagnoses and polydrug involvement, the challenge of habilitation as opposed to rehabilitation, and the need to provide a comprehensive, individualized, adaptable, and multidisciplinary continuum of care that includes inpatient and outpatient treatment and ongoing continuing care.

Appropriate treatment approaches must include the recognition that chemical dependence in an adolescent manifests itself in a unique fashion when compared with that in an adult. That a young person may have other diagnoses which are psychiatric in nature must also be recognized. The overall goal of treatment should be to assist these young people in living chemically free and growing along healthier, more adaptive channels. With the proper treatment of an addictive disease and the concurrent emotional and behavioral problems, the chemically abusing or dependent adolescent can resume a productive life free of all mood-altering chemicals. An effective treatment philosophy is based on the idea that successful recovery and successful living can be achieved and maintained through active participation in the 12-step programs. All successful treatment services appear to be based on this approach.

## Recovery

The equation of recovery is as follows:

Sobriety = Abstinence + Tools of Recovery

Both the initial and the long-term goal of recovery is the maintenance of sobriety. With adolescents the equation is modified:

Recovery-Sobriety =
Abstinence + Habilitation + Tools of Recovery + Extended Care

Drug abstinence is a prerequisite for using the tools made available through Alcoholics Anonymous or Narcotics Anonymous, or both, and the treatment facility regimen. The spiritual program that is offered by these groups consists of 12 steps, each of which is "worked" until the adolescent understands it and applies it to daily living situations. As with other special groups, adolescents are thought to need an extended period of support and supervision—called aftercare, extended care, continuing care, or recovery maintenance—during which they adjust to conditions related to reentering life outside the structured treatment program. Continued follow-up through individual and group contact is necessary for one to two years.

Extended care is a necessary condition for recovery in most adolescents because of their age, immaturity, general lack of nonchemical coping skills, and the emotional and developmental lag that occurs owing to prolonged drug use during a time of supposed emotional maturation.

## Diagnosis and Symptoms

The symptoms of drug abuse and addiction are recognizable, diagnosable, and treatable. Adolescent drug use, abuse, and dependence are parts of a continuum, the progression of which is preventable. As with other diseases, results are better if intervention occurs early. It is realistic to expect recovery from drug dependence, particularly in adolescents. Physicians can do much to help at all stages.

Before physicians can become involved in prevention and intervention, awareness of the frequency of drug use among teens is crucial. Because there are more than 23 million teenagers in the 12- to 17-year range—of whom, currently, 3.5 million smoke cigarettes, 2.8 million use marijuana, and 6.2 million use alcohol—it is highly likely that most physicians see many drug users, more than a few abusers, and some who are dependent. Drug abuse is a problem that affects children all across the country, in all socioeconomic classes.[2] Physicians should also be aware that all mood-altering substances can be highly addictive and that even an

initial experimentation with tobacco and alcohol can lead to more serious dependence.

All too often, drug abuse or addiction goes unrecognized by physicians. Accidents and injuries suffered by teenagers should suggest the possibility of alcohol or other drug abuse. Physicians who are alert and informed will consider drug abuse in the adolescent who comes to the office with symptoms such as cough, sore throat, conjunctivitis, chronic infections, or respiratory complaints. A drop in grades, a loss of interest in school, and behavioral and emotional problems are common symptoms of advancing drug abuse but usually are not recognized by parents as being drug-related. Psychoactive drug use by adolescents must always be considered in the differential diagnosis of general health or emotional problems, poor appetite, insomnia, depression, or loss of energy and motivation.

Health professionals must understand chemical dependence not only as a chronic and progressive disease but, more important, as a treatable disease. An early and accurate diagnosis leads to an increased chance for success of intervention and treatment. Many symptoms of certain drugs in adolescents can be easily misdiagnosed for psychiatric illness. Treating the observed symptom may be different from treating the drug abuse. Polydrug abuse in an adolescent further complicates the clinical picture, especially when the treating physician is unaware of the drug abuse of the patient. In addition, the younger the age that a person has exposure to a chemical, the more susceptible that person is to a psychiatric reaction.[12] The early stages of adolescent drug use may also be missed because behavioral changes may be attributed incorrectly to the normal maturation process that occurs during adolescence.[13] For these reasons, drug abuse testing, such as urine drug screening, is essential to provide the proper treatment for the diagnosed condition.[14]

Pediatricians and other primary health care providers are particularly in a position to address substance abuse and dependence prevention from a developmental perspective. They can play a notable role in informing and educating the family and the community about alcohol and drug problems. Parents, students, schools, law enforcement officials, and others may turn to physicians for assistance. Physicians must be aware of the community resources such as substance abuse prevention and treatment programs, parent action groups, self-help groups, and community-mobilized efforts to combat chemical abuse and dependence.

Early diagnosis and intervention with youth can result in enormous benefits to them, their families, and to society.

## REFERENCES


1. King P: Sex, Drugs and Rock 'n Roll. Bellevue, Wash, Professional Counselor Book, 1988
2. MacDonald DI: Patterns of alcohol and drug use among adolescents. Pediatr Clin North Am 1987; 34:275-288
3. Johnston L, O'Malley P, Bachman J: Drug Use Among American High School Students, College Students, and Other Young Adults. Washington, DC, Dept of Health and Human Services, 1986
4. Kandel DB, Logan JA: Patterns of drug use from adolescence to adulthood: Periods of risk for initiation, continued use, and discontinuation. Am J Public Health 1984; 74:660-666
5. Morrison MA, Smith QT: Psychiatric issues of adolescent chemical dependence. Pediatr Clin North Am 1987; 34:461-480
6. Schaefer D: Choices and Consequences. Minneapolis, Minn, Johnson Institute Press, 1987
7. Semlitz L, Gold MS: Adolescent drug abuse: Diagnosis, treatment, and prevention. Psychiatric Clin North Am 1986; 9:455-473
8. Wheeler K, Malmquist J: Treatment approaches in adolescent chemical dependence. Pediatr Clin North Am 1987; 34:437-448
9. Gordon NP, McAlister A: Adolescent drinking: Issues and research, *In* Coates TJ (Ed): Promoting Adolescent Health: A Dialogue in Research and Practice. New York, Academic Press, 1982
10. Talbott GD: Substance abuse and the professional provider. Alabama J Med Sci 1986; 21:150-155
11. Talbott GD: Alcoholism and other drug addictions: A primary disease entity. J Med Assoc GA. 1986; 75:490-494
12. Estroff TW, Gold MS: Psychiatric presentations of marijuana abuse. Psychiatric Ann 1986; 16:221-224
13. MacDonald DI, Czechowicz D: Marijuana: A pediatric overview. Psychiatric Ann 1986; 16:215-218
14. Verebey K, Gold MS, Mulé SJ: Laboratory testing in the diagnosis of marijuana intoxication and withdrawal. Psychiatric Ann 1986; 16:235-241

Addiction Medicine
and the Primary Care Physician

# Drug Abuse, Psychiatric Disorders, and AIDS

## Dual and Triple Diagnosis

STEVEN L. BATKI, MD, *San Francisco*

*Substance abuse and psychiatric disorders commonly occur together. This form of dual diagnosis is notable because it complicates assessment and makes treatment more difficult for both psychiatric and drug abuse problems. Drugs can cause psychiatric disorders and can also be used as an attempt to "cure" them by self-medication. The spread of the human immunodeficiency virus (HIV) among drug users has added a third potential clinical problem, that of the aquired immunodeficiency syndrome, to the difficulties already presented by drug abuse and psychiatric disorders. Patients with this triple diagnosis pose challenges to primary care physicians as well as addiction medicine specialists or psychiatrists. Assessment should include a drug abuse history, preferably corroborated by others, evaluation of the mental state, and examination focusing on signs of drug abuse and HIV infection. Treatment should include the management of HIV disease, abstinence from drug abuse, and access to psychiatric care. New systems of health care service, including interdisciplinary case management, may be needed to manage patients with a triple diagnosis.*

(Batki SL: Drug abuse, psychiatric disorders, and AIDS—Dual and triple diagnosis, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:547-552)

The clinical problems of drug abuse are frequently complicated by the presence of other psychiatric disorders. The term "dual diagnosis" refers to the joint presentation of psychiatric problems and drug abuse. A dual diagnosis can involve all classes of drugs of abuse and numerous psychiatric disorders, including depression, anxiety, and psychosis (Table 1). Patients with a dual diagnosis are seen by psychiatrists, addiction medicine specialists, or primary care physicians. A dual diagnosis is important for several reasons: it has a high prevalence, it makes assessment less clear, and it makes treatment more difficult. The growth of the acquired immunodeficiency syndrome (AIDS) as a medical problem among drug users has led to additional difficulties in diagnosing and treating a patient with psychiatric problems and drug abuse. These patients with a "triple diagnosis" pose a new set of dilemmas to clinicians engaged in psychiatric, medical, or drug abuse treatment. Their needs challenge the resources of these separate treatment systems and require the creation of new systems of care that cross the boundaries of these disciplines.

### Case Example of Dual Diagnosis

The patient, a 40-year-old single Latino man in methadone maintenance treatment, gradually became anxious, suspicious, hostile, and threatening a year after entering treatment. Paranoid delusions—of being followed, observed, and talked about—became increasingly prominent. On psychiatric examination the presence of these delusions was affirmed; also noted were tremulousness, diaphoresis, and hypervigilance. The patient described a history of "paranoid schizophrenia" reported to have been diagnosed ten years previously when he was in jail. Further history-taking revealed chronic benzodiazepine dependence, with a self-reported use of 60 mg to 100 mg of diazepam a day, which had been recently interrupted because of the patient's inability to maintain the source of his illicit supply. A detailed history suggested that all past episodes of psychosis were related to withdrawal from benzodiazepines. Treating the patient's psychosis required abstaining from benzodiazepines and using phenobarbital, 180 mg a day, tapered over 12 weeks, leading to a resolution of symptoms. Urine screening was needed to monitor for the recurrence of illicit benzodiazepine use, and the patient required periodic psychiatric evaluation to monitor his mental state.

### Patterns of Dual Diagnosis

The problems of patients with coexisting drug abuse and psychiatric disorders can be characterized as belonging to one of three basic patterns. In the first pattern—drugs as the cause—drug use is considered to be primary, causing a psychiatric disorder. Drug use can cause psychiatric symptoms acutely, such as during intoxication with cocaine or other stimulants, producing hallucinations and paranoid delusions. Drug-related psychoses of this type are usually brief in duration but can occasionally last for weeks. Continuous drug use can cause long-lasting psychiatric disorders, as in alcohol-associated dementia and other organic brain disorders.

From the Department of Psychiatry, University of California, San Francisco, School of Medicine, and the Substance Abuse Services, San Francisco General Hospital Medical Center.

This work was supported in part by National Institute on Drug Abuse grant No. R18 DA06097 and grant No. DA01696.

Reprint requests to Steven L. Batki, MD, Medical Director, Substance Abuse Services, San Francisco General Hospital Medical Center, 1001 Potrero Ave, San Francisco, CA 94110.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ARC = AIDS-related complex
HIV = human immunodeficiency virus
IV = intravenous

TABLE 1.—*Drug Classes and the Effects of Associated Psychiatric Disorders*

| *Drug Class* | *Anxiety Disorders* | *Mood Disorders* | *Psychosis* |
|---|---|---|---|
| CNS depressants ..... | ++++ | +++ | ++ (in severe withdrawal) |
| CNS stimulants ..... | +++ | +++ | +++ (in severe intoxication) |
| Hallucinogens..... | ++ | ++ | ++++ |
| Opiates ..... | +++ | ++++ | + |

CNS=central nervous system, ++++=very frequent, +++=frequent, ++=occasional, +=rare

A second pattern—drugs as cure—occurs in patients whose preexisting psychiatric disorders lead to drug or alcohol use as an attempt to self-medicate the symptoms of anxiety, depression, or psychosis. An example is a depressed patient who attempts to medicate a mood disorder with stimulants such as cocaine. Depressive disorders may actually become more severe as drug tolerance, dependence, and, potentially, drug withdrawal effects set in. Self-medication can lead to worsening of the psychiatric symptoms that led to drug use in the first place. New evidence of the increased risk of drug use among patients with psychiatric problems was described in the recent work of Christie and collaborators, who reported that young adults with depressive or anxiety disorders had twice the risk of other young people for subsequent substance abuse.[1] Although drug use can lead to a psychiatric disorder, and vice versa, most often the primary care physician is presented with a third dual diagnosis pattern—that of simultaneous or parallel presentation. Most often, the "chicken-egg" question of what came first—drug abuse or psychiatric disorder—cannot reliably be answered.

## Prevalence of Dual Diagnosis

Recent studies have shown a high prevalence of psychiatric disorders among certain groups of drug users. For example, heroin addicts have been particularly well studied, notably in large-scale investigations at Yale and Harvard.[2,3] The investigators report psychiatric disorders other than drug abuse to occur at a lifetime prevalence in the 77% to 87% range. The most common psychiatric problems were mood disorders—primarily depression—and anxiety disorders. Depression was present in more than 50% of heroin addicts—about five times the prevalence seen in the population as a whole. Ross and co-workers examined both drug abusers and alcoholics and found a similarly high prevalence of psychiatric disorders.[4]

Another way to look at the prevalence of a dual diagnosis is to examine the rates of drug use among psychiatric patients. Such studies have found much higher rates of drug and alcohol problems among psychiatric patients than among the rest of the population. Psychiatric outpatients have high rates of substance abuse, ranging from 17% to 53%, with emergency department patients having the highest rate among outpatients.[5,6] Psychiatric inpatients have even higher rates of drug or alcohol problems, ranging from 32% to 63%.[7,8] In these studies, younger and more severely ill patients had higher rates of dual diagnoses.

## Assessment of Dual Diagnosis

Patients with a dual diagnosis may be more likely to seek care from primary care physicians for complaints of somatic or psychiatric problems than for direct complaints about their drug or alcohol use. Denial, long noted to be the major psychological defense used by drug abusers, makes it important for physicians to have a high index of diagnostic suspicion and a willingness to consider the presence of drug or alcohol use. A diagnosis of drug abuse rests on the same basic elements as in any other area of medicine—history, physical examination, and, when appropriate, laboratory tests. A complete history is crucial and should include asking patients in a nonjudgmental, concerned, and compassionate manner about their drug and alcohol use. Questions should include basics such as drug or drugs of choice, duration, frequency, and amount of drug use. It is essential to ask about the route of drug administration, as infection with the human immunodeficiency virus (HIV) is a major risk associated with intravenous drug use. Perhaps the single most important aspect of taking a drug abuse history, however, is to get corroborative information from another source, such as a family member or another health care provider, because patients will tend to minimize or deny their problems with drugs or alcohol. The physical examination and clinical laboratory studies also have important roles. Examination can reveal the physical stigmata of drug or alcohol use, such as injection marks, damage to the nasal septum from intranasal drug use, or the many signs of alcohol-related liver disease. Laboratory testing can give important indirect indicators of drug use, such as signs of liver disease or increased mean cell volume in the case of alcohol abuse. Laboratory test results can also give direct evidence, as in the use of urine toxicology screens for drugs of abuse. Urine testing should be done with a patient's consent whenever possible, and results should be treated with particular care as to confidentiality. A mental state evaluation should pay particularly close attention to the presence of any psychiatric symptoms of an abrupt onset, particularly confusion, panic, delusions, and hallucinations. Hallucinations that are visual and tactile tend to be especially common in drug-induced states. A psychiatric consultation should be part of the evaluation of patients with psychotic symptoms or hallucinations.

## Dual Diagnosis and Treatment Outcome

The prognosis for dual diagnosis patients is worse than for patients with either disorder by itself. Patients with coexistent drug problems had poor treatment outcomes in a 1977 study of outpatient psychotherapy by Hall and co-workers.[9] Psychiatric outcome may be particularly grave among depressed drug users and can include suicide. Algulander and colleagues found an 8% rate of suicide among sedative-hypnotic drug abusers in Sweden in the four to six years after these patients completed a hospital-based detoxification program.[10] High suicide rates were also noted in another Swedish study of more than 1,300 alcoholics who were observed for as long as 30 years.[11] Among these patients, fully 17% of all deaths during the follow-up period were by suicide.

A dual diagnosis does not only affect psychiatric treatment outcome, but it also lowers the chance of success in drug abuse treatment. Drug abusers or alcoholics with psy-

chiatric disorders—most notably depression—do less well and have a higher dropout rate from drug abuse treatment.[12,13] The higher likelihood of treatment failure has especially serious implications for HIV-infected patients whose continued drug use poses risks to their own and to public health.

## Case Example of Triple Diagnosis

The patient, a 35-year-old white married woman, entered methadone maintenance treatment with a diagnosis of asymptomatic HIV infection. She did well in methadone treatment for the first year but then began to have headaches, depression, irritability, and violent behavior toward her husband. Her psychiatric deterioration was associated with episodes of relapsing to drug abuse. Eventually, she experienced auditory hallucinations and suicidal ideation that necessitated her being admitted to hospital. Results of a computed tomographic scan of the head showed intracranial lesions consistent with toxoplasmosis. Treating her with pyrimethamine and sulfadiazine led to improvement, but her psychiatric symptoms continued and required antipsychotic treatment with haloperidol.

## Triple Diagnosis—AIDS, Drug Use, and Psychiatric Disorders

Intravenous drug users are an increasingly important group among HIV-infected patients. The proportion of AIDS patients with intravenous (IV) or other injection drug use as a risk factor—either alone or in combination with homosexual or bisexual behavior—has increased to 27%.[14] The role of drug use in AIDS extends beyond simply transmitting the human immunodeficiency virus through injection. Another way in which drug use may be involved in the spread of HIV is through drug-induced disinhibition of behavior, mainly in the form of intoxication-related hypersexuality due to stimulant use, as well as through unsafe, promiscuous sexual behavior in sex-for-drugs transactions that can accompany drug use.[15] The chaotic and impulsive life-style associated with drug use contributes to a disregard for safety in sexual behavior or in the hygiene of drug use itself. In addition, drug use may be a cofactor for HIV by lowering resistance to the virus through impairing cell-mediated immunity. Drugs implicated in immune suppression include the opiates, cocaine, alcohol, marijuana, and others.[16] In a person infected with HIV, drug use may add to the risk of the development of many of the forms of morbidity associated with the virus. Continued parenteral drug use may stimulate HIV activation and replication[17] and also places users at risk for secondary infections. Finally, psychopathology associated with drug use may complicate and further exacerbate the neuropsychiatric and mental health problems associated with AIDS itself.

Education about HIV and drug abuse is a crucial part of AIDS prevention. The goal of education is to reduce AIDS-risk behaviors by giving two basic messages—safe sex and no needle sharing. Promoting safe sex requires more than simply distributing condoms. Attitudes about sexuality, culturally defined sex roles, and lack of information about the sexual transmission of AIDS are all areas that need to be addressed through education and counseling. Counseling is neccessary to help teach sexual partners of IV drug users how to communicate their requests for safe sex in ways that will increase the chances for behavioral change. Teaching safe needle use is another AIDS prevention strategy. Intravenous drug users can be taught to avoid sharing needles and to use bleach or other methods of needle cleaning.[18] Educational approaches may have the greatest potential for benefit if they are coupled with actual hands-on instruction that includes the teaching of needle cleaning and demonstrations of proper condom use. In San Francisco, such community education efforts may be making their effect felt among drug users. For example, the proportion of patients at the detoxification clinic at San Francisco General Hospital Medical Center who reported sharing needles dropped significantly between 1986 and 1988.[19]

## AIDS and Drug Abuse Treatment

Drug abuse treatment is essential for HIV-infected IV drug users for several reasons. Drug abuse treatment for this group must be recognized as a form of AIDS prevention, achieved through reducing needle use and needle sharing secondary to a decrease in drug use brought about by such treatments as methadone maintenance.[20] Prevention may also be an indirect outcome of the reduction of impulsive, unsafe sex acts associated with intoxicated, disinhibited states. Moreover, drug abuse treatment is important in that it provides a setting for delivering other services needed by HIV-infected persons, including psychiatric care, medical care, social services, and AIDS education. Drug abuse treatment may also be helpful in reducing the morbidity associated with HIV infection, perhaps through decreasing the assaults on the immune system and reducing exposure to infectious agents.[21]

Drug abuse treatment programs can be broadly categorized as one of three methods: self-help, residential treatment, and medical treatment.[22] Treating HIV-infected patients in any of these ways presents a number of problems as well as opportunities and requires the use of novel strategies. Self-help programs, such as Alcoholics Anonymous or Narcotics Anonymous, are free of charge and are nearly universally available.[23] These groups are extremely valuable in offering support for sobriety and abstinence. These 12-step programs have a strong recovery orientation and a philosophy that emphasizes a medication-free approach to treatment that can be difficult for a dual diagnosis patient receiving pharmacotherapy. An important future direction for self-help programs may be the development of specialized 12-step groups for both psychiatric patients and those with HIV infection.

A second treatment method, residential drug abuse programs, is rooted in the therapeutic community model originated by such seminal programs as New York City's Daytop Village and Phoenix House. These programs offer a long-term residential setting designed to produce behavioral changes in a drug user. The principles of treatment include the use of peer support, confrontation, and behavior-shaping through the use of milieu-based rewards and punishments. Residential programs have recently begun to address the special problems of treating HIV-infected clients.[24] In New York and San Francisco, programs have attempted to create special treatment approaches for these persons. A number of difficult problems can complicate treatment, however. It can be hard to motivate HIV-infected patients to seek admission to residential programs because of their high demands and extended treatment needs. Many HIV-infected drug users have a sense of hopelessness[25] and may lack the optimistic sense of an open-ended future that can be necessary to make

long-term therapeutic commitments. Residential programs, therefore, need to increase their flexibility and lower their thresholds for admitting HIV-infected clients.

There are other problems facing residential programs as they attempt to work within the framework of the AIDS epidemic. In general, a recurrent question is to what degree to subordinate the needs of the community to the medical and psychological needs of a person with AIDS or the AIDS-related complex (ARC).

Medical interventions are a third type of substance abuse treatment applicable to HIV-infected drug users. These programs use a medical model, involve physicians and other health care professionals, and frequently offer the use of medication. Pharmacologic approaches are available for most classes of drugs, such as benzodiazepines for alcohol withdrawal, antidepressants and other agents for cocaine dependence, and clonidine hydrochloride, naltrexone hydrochloride, or methadone hydrochloride for the treatment of opiate dependence.

The treatment of stimulant abuse may be particularly important for preventing AIDS. Because of the short duration of its effect, cocaine must be readministered frequently, increasing the user's exposure to potentially contaminated needles. Cocaine use has been implicated as an especially important risk factor for HIV infection for intravenous drug users.[26] Pharmacotherapy for cocaine is still problematic. While some studies of antidepressant drugs have been promising,[27] others have failed to replicate the usefulness of desipramine hydrochloride for cocaine abuse, particularly in methadone maintenance patients.[28] Other investigators have looked to dopamine agonists such as the antiparkinsonian drugs amantadine hydrochloride and bromocriptine mesylate to decrease the postabstinence craving for cocaine.[29] To date, however, while both antidepressants and antiparkinsonian drugs are useful, there is no firm evidence to support the uniform application of one treatment over the other. Medications are important adjuncts, but psychosocial interventions remain crucial to cocaine abuse treatment.

By far the largest treatment method for intravenous drug users follows a medical model—methadone maintenance treatment. Methadone is generally effective in greatly reducing IV opiate use and its associated criminality.[20,30] Methadone maintenance treatment offers a number of benefits for HIV-infected patients. It offers a long-term, stable treatment setting within which medical, psychiatric, and social services can be offered in addition to substance abuse treatment.[31]

Substance abuse treatment of HIV-infected IV opiate users requires greater flexibility than is provided by traditional treatment approaches. Patients infected with HIV generally have far more psychosocial problems than other drug users.[32] Psychological distress is high, and depression and suicidality are prominent. Among HIV-infected patients entering treatment at San Francisco General Hospital's Substance Abuse Services, for example, 13% reported suicide attempts in the month before admission.[33] Distress in these proportions makes substance abuse treatment more difficult. These patients may therefore need more time than other addicts to "clean up" their drug use.[34] Another area needing flexibility is the duration of treatment. Methadone treatment programs, for example, traditionally have encouraged their patients to try to taper off methadone and eventually live drug-free lives. Unfortunately, discontinuing methadone treatment is rarely successful for extended periods of time, and most addicts resume drug use after stopping methadone treatment. For HIV-infected patients, the personal and public health costs of getting off methadone treatment may be too high. Flexibility is also needed in terms of increased tolerance for behavioral problems, although the line must be drawn at violent or threatening behavior. Even HIV-infected patients may have to face discharge if continuation in treatment is judged to be dangerous to patients or staff or harmful to a treatment program as a whole.

### Counseling for HIV-Infected Drug Users

Counseling specific to AIDS must be part of treatment programs for IV drug users. A basic component of such counseling is education concerning safe sex and the importance of avoiding the sharing of needles. Counseling departs from the usual substance abuse treatment in a number of ways. Family and couples counseling may be necessary to help patients and their families come to terms with the changes associated with HIV disease. Grief counseling is an important part of helping patients to cope with the deaths of friends or spouses and with the fear of their own illness or death. Patients need the opportunity to deal with feelings of grief about other losses such as the inability to work or the loss of sexuality.[32] Individual counseling aimed at these difficult issues can be supplemented by referring patients to support groups designed to meet some of the special needs of HIV-infected patients. Support groups that are extremely helpful are those that address the special needs of heterosexual drug-using patients, women, and minorities.

Drug abuse treatment of HIV-infected patients is complicated by the severity of their psychiatric problems. It can be difficult to motivate HIV-infected patients, who frequently suffer from anxiety, depression, or demoralization, possibly combined with physical discomfort. Appeals to altruism and to self-interest are two counseling strategies that may help to motivate these patients. The former can be addressed in didactic counseling that teaches IV drug users that sharing needles can spread the human immunodeficiency virus from the patient to others such as friends and family. This message is essentially: "Don't use drugs because you may spread AIDS to others." The second approach—appeal to self-interest or the preservation of health—is also presented in didactic counseling. It addresses the likelihood of increased morbidity associated with continued drug use, based on the probability that continued parenteral exposure to foreign antigens may be an activating cofactor for HIV[17] and on some tentative clinical evidence that decreased drug use may be associated with decreased morbidity in infected IV drug users.[21]

Medical, psychiatric, and social services are areas in which HIV-infected IV drug users have far greater needs than "healthy" addicts. Drug abuse treatment programs traditionally have had the resources to provide only the bare minimum of such services. This minimum is no longer enough when drug abuse treatment programs face a severely ill and increasingly disabled population. These persons have a difficult time making and keeping the numerous appointments with various health care and social service providers involved in their treatment. This means that drug programs must do more to establish liaisons with other treatment providers and may need to provide ancillary services on site. Examples are providing psychiatric evaluation and treatment and AIDS-related medical care on site at drug programs. Such services,

by providing better day-to-day care for HIV-infected IV drug users, may reduce the number or severity of psychiatric and medical crises that otherwise may require a hospital stay.

Despite concerns that the increased severity of problems faced by these patients might reduce the effectiveness of methadone maintenance treatment, the experience of the San Francisco General Hospital PACE program has been promising. The first 29 HIV-infected patients prospectively evaluated showed significant decreases in several measures of drug use. After three months of methadone maintenance treatment, overall IV drug use decreased from an average of 29 days a month to fewer than 6 days.[33]

## Treating Drug Users Who Have Dual and Triple Diagnoses

The initial approach to treating psychiatric problems in the presence of drug abuse and HIV infection should follow the basic principles of treating patients with a dual diagnosis. Addressing the problem of drug or alcohol use is the first step in this approach (Table 2). Abstinence from drugs or alcohol is an essential part of treating the psychiatric symptoms of these patients. Helping patients achieve abstinence is too big a job for the physician to take on alone. Patients must be encouraged to participate in drug abuse treatment, particularly in self-help programs. Education is essential and should focus on teaching patients about the likely connection between drug or alcohol use and their psychiatric disorder as well as HIV disease. The treatment of dual diagnoses should include monitoring not only psychiatric symptoms but drug or alcohol abuse as well. Substance abuse is a chronic disorder, so the primary care practitioner must always keep in mind the possibility of relapse to drug abuse in a patient with dual diagnoses. When AIDS, ARC, or asymptomatic HIV infection is added to drug abuse, the risks for psychopathology increase. There are a number of common sources of psychological distress among drug users with HIV disease. These stressors are similar to those faced by non-drug-using HIV-infected patients, but they can be more intense because of the special vulnerabilities of drug users. Some sources of distress include the awareness of a terminal illness, losses of health and sexuality, isolation and ostracism, and the negative attitudes or countertransference of health care providers. Psychiatric problems are particularly important in that they can exacerbate drug use. The poor coping skills and ego deficits noted in these patients may lead them to respond to the added stresses of illness by increasing their drug use.[35,36] Drug users may lack other effective adaptive mechanisms to counter the dysphoria that can result from stress.

Preexisting psychopathology is only one of the many contributors to the mental health problems of HIV-infected drug users, however. Other factors include continued drug use, with its acute and chronic psychiatric sequelae, and HIV itself—through direct effects such as HIV encephalopathy and indirect effects such as secondary infections or neoplasms involving the central nervous system. The psychosocial factors associated with AIDS, such as isolation, ostracism, and the many losses, are yet another layer of additive stress that contributes to mental health problems. The psychological themes voiced by these patients include denial, anger and antisocial behavior, depression, isolation, and continued drug abuse.[32]

Psychiatric disorders have been encountered in most HIV-infected drug users in treatment at San Francisco General Hospital. A chart review of psychiatric consultations among the first 49 HIV-infected patients at the Substance Abuse Services showed that 84% had a psychiatric diagnosis, with 33% having depressive disorders, 33% having anxiety disorders, and organic brain disorders found among 18%.[37] Psychiatric disorders among drug users are particularly important in that they are associated with a worse outcome for drug abuse treatment and, by extension, possibly greater risks of spreading HIV. The severity of psychiatric illness in drug users has previously been shown to be a predictor of a poor outcome in drug abuse treatment.[38] Research at San Francisco General Hospital strongly suggests that this relationship also holds true for HIV-infected IV drug users. In a prospective study of drug abuse treatment outcome, the presence of depression, hopelessness, and suicidality at intake into treatment of HIV-infected patients was predictive of a worse outcome in terms of heroin, cocaine, and total intravenous drug use a year later.[25] The presence of suicidal thoughts or attempts before coming into treatment was especially strongly associated with a poor treatment outcome.

TABLE 2.—*Management of Dual Diagnosis of Drug Abuse and Psychiatric Disorders*

- Abstinence from drugs and alcohol
- Patient education about drugs and psychiatric disorders
- Drug abuse treatment, especially self-help programs such as Alcoholics Anonymous
- Supportive psychotherapy
- If medication is needed, use nonaddictive agents
- Monitor for relapse to drug or alcohol abuse, or both, and employ confrontation
- Close communication with other health care providers

TABLE 3.—*Management of Triple Diagnoses of Drug Abuse, Psychiatric Disorders, and AIDS*

- Providing material supports: food, housing, and medical care
- Education about AIDS
- Self-help HIV support groups specific to drug users
- Supportive psychotherapy
- Psychiatric medication, attempting to avoid abusable medications
- Residential treatment or admission to hospital if necessary to protect the patient or others
- Case management

AIDS=acquired immunodeficiency syndrome, HIV=human immunodeficiency virus

Managing the mental health problems seen in HIV-infected drug users involves different levels of intervention (Table 3). Perhaps the most important of these interventions is providing material supports. Patients recently diagnosed as being HIV-seropositive or having ARC or AIDS can experience high levels of distress associated with uncertainty about their disease: its severity, its time course, and its treatments. Anything that reduces this uncertainty may help them. Assisting with housing, welfare funds, meals, transportation, and health care may all have the effect of reducing uncertainty and its attendant anxiety.

Another type of intervention consists of providing information to reduce feelings of uncertainty and helplessness. Self-help groups are also important in reducing isolation but may be difficult to provide for drug users, who may not have a supportive community of peers. Supportive psychotherapy

can bolster psychological defenses and, it is hoped, reduce the need to use drugs. Psychiatric medications may be needed to treat serious mood and anxiety disorders, organic disorders, and psychosis. The keystone of pharmacologic management of HIV-infected intravenous drug users is safety. Medications must not be allowed to increase morbidity by adding adverse effects to the problems associated with AIDS and drug abuse. Furthermore, drug users may not be able to safely handle potentially abusable medications such as benzodiazepines and psychostimulants. An example of a nonaddictive medication with a relatively low incidence of adverse effects is buspirone hydrochloride, which may be useful as an alternative to the benzodiazepines in treating anxiety in HIV-infected drug users.[39]

When outpatient strategies fail, residential treatment may be required in the form of halfway houses or other alternatives to hospital treatment. If these are inadequate, hospital admission may be needed to protect the patient or others or to support the patient who cannot provide for basic self-care needs.

It may be of value to apply the concept of case management to the care of patients with drug use, HIV infection, and psychiatric disorders. Case management involves combining assessment and treatment planning with linkage to community resources, consultation to agencies, collaboration with institutions, and patient advocacy.[40] Psychiatric interventions may need to follow a case management model, as patients tend to require frequent contacts, extensive networking with different agencies, and negotiation with a variety of service providers. It is often difficult to find treatment settings that can handle the concurrent presentation of psychiatric disorder, drug abuse and its related antisocial behaviors, and medical problems.

## Conclusion

Caring for drug users with a dual and triple diagnosis is a growing challenge. Primary care physicians need to be aware of the possibility of drug abuse when evaluating a patient with psychiatric symptoms or HIV disease. An adequate assessment greatly increases the chances for the appropriate management of these disorders. Arranging for medical, psychiatric, and substance abuse treatment, monitoring drug use, avoiding the prescribing of abusable medications, and communicating with other treatment providers are important cornerstones in the primary care of patients with dual and triple diagnoses. Further work is urgently needed to develop more effective models of the treatment of drug users with psychiatric disorders and AIDS.

### REFERENCES


1. Christie KA, Burke JD Jr, Regier DA, et al: Epidemiologic evidence for early onset of mental disorders and higher risk of drug abuse in young adults. Am J Psychiatry 1988; 145:971-975

2. Rounsaville BJ, Weissman MM, Kleber H, et al: Heterogeneity of psychiatric diagnosis in treated opiate addicts. Arch Gen Psychiatry 1982; 39:161-168

3. Khantzian EJ, Treece C: DSM-III psychiatric diagnosis of narcotic addicts: Recent findings. Arch Gen Psychiatry 1985; 42:1067-1071

4. Ross HE, Glaser FB, Germanson T: The prevalence of psychiatric disorders in patients with alcohol and other drug problems. Arch Gen Psychiatry 1988; 45:1023-1031

5. Mezzich JE, Fabrega H, Coffman GA, et al: DSM-III disorders in a large sample of psychiatric patients: Frequency and specificity of diagnoses. Am J Psychiatry 1989; 146:212-219

6. Atkinson RM: Importance of alcohol and drug abuse in psychiatric emergencies. Calif Med 1973; 118:1-4

7. Fischer DE, Halikas JA, Baker JW, et al: Frequency and patterns of drug abuse in psychiatric patients. Dis Nerv Syst 1975; 36:550-553

8. Fernandez-Pol B, Bluestone H, Mizruchi M: Inner city substance abuse patterns: A study of psychiatric inpatients. Am J Drug Alcohol Abuse 1988; 14:41-50

9. Hall RCW, Popkin MK, Devaul RA, et al: The effect of unrecognized drug abuse on diagnosis and therapeutic outcome. Am J Drug Alcohol Abuse 1977; 4:455-465

10. Allgulander C, Borg S, Vikander B: A 4-6-year follow-up of 50 patients with primary dependence on sedative and hypnotic drugs. Am J Psychiatry 1984; 141:1580-1582

11. Berglund M: Suicide in alcoholism: A prospective study of 88 suicides—1. The multidimensional diagnosis at first admission. Arch Gen Psychiatry 1984; 41:888-891

12. Rounsaville BJ, Weissman MM, Crits-Cristoph K, et al: Diagnosis and symptoms of depression in opiate addicts—Course and relationship to treatment outcome. Arch Gen Psychiatry 1982; 39:151-156

13. McLellan AT, Luborsky L, Woody GE, et al: Predicting response to alcohol and drug abuse treatments—Role of psychiatric severity. Arch Gen Psychiatry 1983; 40:620-625

14. Centers for Disease Control: HIV/AIDS Surveill Rep 1989; (Dec):1-16

15. Fullilove RS, Fullilove MT, Bowser BP, et al: Crack use and risk for AIDS among black adolescents. Presented at the 5th International Conference on AIDS (Abstract WDP61), Montreal, June 1989

16. MacGregor RR: Alcohol and drugs as co-factors for AIDS. *In* Siegel L (Ed): AIDS and Substance Abuse. New York, Harrington Park Press, 1988

17. Zagury D, Bernard J, Leonard R, et al: Long-term cultures of HTLV-III-infected T-cells: A model of cytopathology of T-cell depletion in AIDS. Science 1986; 231:850-853

18. Sorensen JL, Gibson D, Heitzmann C, et al: Pilot trial of small group AIDS education with intravenous drug abusers. *In* Harris LS (Ed): Problems of Drug Dependence, 1988. Natl Inst on Drug Abuse Res Monogr Ser 1988; 90:60

19. Sorensen JL, Guydish J, Costantini M, et al: Changes in needle sharing and syringe cleaning among San Francisco drug abusers (Letter). N Engl J Med 1989; 320:807

20. Ball JC, Lange WR, Myers CP, et al: Reducing the risk of AIDS through methadone maintenance treatment. J Health Soc Behav 1988; 29:214-226

21. DesJarlais DC, Friedman SR, Marmor M, et al: Development of AIDS, HIV seroconversion, and potential cofactors for T4 cell loss in a cohort of intravenous drug users. AIDS 1987; 1:105-111

22. Klein JM, Miller SI: Three approaches to the treatment of drug addiction. Hosp Community Psychiatry 1986; 37:1083-1085

23. Nichols H: Narcotics Anonymous. J Subst Abuse Treat 1988; 5:195-196

24. Goldstein MJ, Yuen FM: Coping with AIDS: An approach to training and education in a therapeutic community—The Samaritan Village program. J Subst Abuse Treat 1988; 5:45-50

25. Batki SL, Sorensen JL, Gibson DR, et al: HIV-infected IV drug users in methadone treatment: Outcome and psychological correlates—A preliminary report. *In* Harris LS (Ed): Problems of Drug Dependence, 1989. Natl Inst Drug Abuse Res Monogr Ser, in press

26. Chaisson RE, Bacchetti P, Osmond D, et al: Cocaine use and HIV infection in intravenous drug users in San Francisco. JAMA 1989; 261:561-565

27. Gawin FH: Chronic neuropharmacology of cocaine: Progress in pharmacotherapy. J Clin Psychiatry 1988; 49(Suppl):11-16

28. Arndt I, Dorozynsky L, Woody G, et al: Desipramine treatment of cocaine abuse in methadone maintained outpatients. *In* Harris LS (Ed): Problems of Drug Dependence. Natl Inst Drug Abuse Res Monogr Ser 1988; 90:347

29. Tennant FS Jr, Sagherian AA: Double-blind comparison of amantadine and bromocriptine for ambulatory withdrawal from cocaine dependence. Arch Intern Med 1987; 147:109-112

30. Senay EC: Methadone maintenance treatment. Int J Addict 1985; 20:803-821

31. Batki SL: Treatment of intravenous drug users with AIDS: The role of methadone maintenance. J Psychoactive Drugs 1988; 20:213-216

32. Batki SL, Sorensen JL, Faltz B, et al: Psychiatric aspects of treatment of I.V. drug abusers with AIDS. Hosp Community Psychiatry 1988; 39:439-441

33. Batki SL, Sorensen JL, Coates C, et al: Methadone maintenance for AIDS-affected IV drug users: Treatment outcome and psychiatric factors after three months. *In* Harris LS (Ed): Problems of Drug Dependence. Natl Inst Drug Abuse Res Monogr Ser 1988; 90:343

34. Sorensen JL, Batki SL, Good P, et al: Methadone maintenance program for AIDS-infected addicts. J Subst Abuse Treat 1989; 6:87-94

35. Khantzian EJ: The ego, the self and opiate addiction: Theoretical and treatment considerations. Int J Psychoanal 1979; 5:189-198

36. Khantzian EJ, Mack JE, Schatzberg AF: Heroin use as an attempt to cope: Clinical observations. Am J Psychiatry 1974; 131:160-164

37. Batki SL: Substance abuse and AIDS: The need for mental health services. *In* Goldfinger SM (Ed): New Directions in Mental Health Services. San Francisco, Jossey-Bass, in press

38. McClellan AT, Luborsky L, Woody GE, et al: Predicting response to alcohol and drug abuse treatments: The role of psychiatric severity. Arch Gen Psychiatry 1983; 40:620-625

39. Batki SL: Buspirone in drug users with AIDS or AIDS-related condition. J Clin Psychopharmacol (suppl), in press

40. Kanter J: Clinical case management: Definition, principles, components. Hosp Community Psychiatry 1989; 40:361-368

**Addiction Medicine**
**and the Primary Care Physician**

# The Treatment of Perinatal Addiction

## Identification, Intervention, and Advocacy

MARTY JESSUP, RN, MS, *Berkeley, California*

*Women of reproductive age who use and abuse psychoactive drugs and alcohol present a special challenge to primary care physicians. There are compelling medical reasons for identifying and intervening with pregnant women who are addicted or have alcoholism. The teratogenicity of all drugs of abuse and alcohol, the risk of infection with the acquired immunodeficiency syndrome (AIDS), and the potential for full recovery of a pregnant woman from addiction are some of the reasons that identification and intervention in the problem are indicated. Whether encountered in the clinic setting or in private practice, chemically dependent pregnant or postpartum women are usually responsive to appropriate physician interventions that include a detailed and caring confrontation- and advocacy-oriented support. Complex legal and ethical issues surround perinatal addiction including the role of toxicologic screening, reports to child welfare services, issues in noncompliance, and interdisciplinary case management.*

(Jessup M: The treatment of perinatal addiction—Identification, intervention, and advocacy, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:553-558)

Pregnancy is a time of change, motivation, and a general orientation by the woman toward behavior that will benefit the developing fetus. For addicted women, however, the continued use of drugs and alcohol despite being pregnant shows one of the behaviors of addictive disease.[1] Chemically dependent women are a highly stigmatized group; the stigma experienced by a pregnant woman addicted to drugs or alcohol is even greater and more vitriolic in nature. Most research in the field of women's chemical dependence treatment suggests that drug or alcohol problems in women are less likely to be recognized; women in whom these problems are recognized are much less likely to be able to find appropriate treatment services that can provide for their needs.[2] Women who do seek treatment are frequently turned down for recovery services simply on the basis of their pregnancy or for having a newborn that they wish to be with in the treatment setting (W. Chavkin, "Help. Don't Jail Drug-Addicted Mothers," *The Oakland Tribune,* July 19, 1989).[3]

Over time, however, it has been effectively shown that comprehensive treatment programs for addicted pregnant women do work.[4-6] Comprehensive services for pregnant addicted women would include obstetric and pediatric care, parenting and childbirth preparation classes, public health nursing visits, and chemical dependence treatment. Woman-oriented treatment services are those that address the specific needs of women in treatment and that reduce barriers to recovery more frequently experienced by women. Therapy for women should also be provided in a style that is acceptable to and accessible by them, taking into account "women's roles, socialization, and relative status within the larger culture."[2] Referral by a primary care physician to chemical dependence treatment and such comprehensive services is only possible when the physician is attuned to the identifying characteristics of addiction in pregnant women. When the diagnosis is suspected, or when there is a "high index of concern" (M. Buxton, oral communication, November 1989), the primary care physician can be instrumental in facilitating the health and well-being of the pregnant addict and her infant.

### Medical, Historical, and Behavioral Indicators

Knowledge of the medical, behavioral, and historical identifying characteristics of addicted or alcoholic pregnant women is the primary task of an intervener when preparing for a treatment-oriented intervention. Additionally, certain history-taking tools with proven reliability may be used effectively during the intake process.

Table 1 lists indicators that may be visible to primary care physicians as consistent with drug or alcohol dependence. No one of these alone is indicative of a problem; rather, they should be viewed as a constellation of items that together may lead to the correct diagnosis of addiction. Indicators must also be interpreted in the context of individual patient status and history.

### Obtaining a History

Women who enter treatment for their chemical dependence or for prenatal care are generally interviewed in some depth relative to their history of drug and alcohol use. Of late, there has been a singular reliance on the technology of urine toxicologic testing as the most appropriate means of identifying a drug or alcohol problem. Still, the most thorough method for obtaining an accurate history is to build a treatment alliance with the patient and then interview for signs and symptoms of addictive disease. The most reliable methods of identification remain the practitioner's individual knowledge of the disease process and the quality of relatedness between patient and physician.

Ms Jessup is President of the California Advocates for Pregnant Women.
Reprint requests to Marty Jessup, RN, MS, 2921 Florence St, Berkeley, CA 94705.

Urine toxicologic testing is certainly a part of the diagnostic process; yet, a sole dependence on this technology can be misleading as it cannot measure the patient's motivation for treatment, the chronicity of her disease, nor her willingness to seek recovery. For explicit history taking, the Drug and Alcohol History (R. Ruggiero, PharmD, Associate Clinical Professor, School of Pharmacy, the University of California, San Francisco, Medical Center, M. Jessup, unpublished data), the Ten Question Drinking History,[7] and the Michigan Alcoholism Screening Test[8] are in wide use and are satisfactorily reliable (Figures 1, 2, and 3).[9,10]

Because the use of any mood-altering chemical during pregnancy has teratogenic potential (though with wide variability in the area of dose-response), these tools are useful in that they measure not only addiction but occasional use as well. Many addicted and alcoholic women enter prenatal care after the third month of their pregnancy, so their physician may think that the history becomes secondary because damage may already have occurred. Though the first trimester is the most vulnerable time for fetal exposure to drugs, there is an "opportunity for catch-up growth and physiologic reconstitution" of the fetus of a woman with alcohol abuse.[7] In addition, some of the effects of opiates, in particular heroin and methadone, can be mediated by good nutritional intake and regular prenatal care. Information obtained in the drug and alcohol interview process becomes data for restatement to the patient in the treatment-oriented intervention process.

## Intervention With the Goal of Treatment

If in the process of completing the drug and alcohol interview the physician becomes aware that the patient has addictive disease, the next step is intervention. This occurs when the physician tells the patient that it is highly likely that she has a drug or alcohol problem and that the physician is recommending treatment of the disease. Because addiction is a primary, progressive, and chronic disease, all efforts should be made to identify and treat it as soon as possible. The physician may convey a sense of hope for recovery to the pregnant woman and act as an advocate for her within the health care system. The intervention has five steps:

- Stating the indicators of a drug or alcohol problem,
- Educating regarding possible effects on the fetus and the benefits of abstinence,
- Expressing concern,
- Referring for treatment, and
- Offering advocacy.

The intervention may be conducted with the following statements:

*Step 1:* You report that you use cocaine on a regular basis. I have observed that you have mood swings, are irritable and agitated, and have difficulty concentrating. You have a chronic rhinitis, and frequently when you come to my office your eyes are glassy and your pupils are dilated. You report that you have intense periods of depression and that your last child was very small for its gestational age. You've men-

TABLE 1.—*Indicators Suggesting Drug or Alcohol Dependence in a Pregnant Woman*

| *Behavioral* | *Medical* | *Historical* |
|---|---|---|
| Vague history regarding personal or medical problems | Liver disease, hepatomegaly | Alcohol- or drug-abusing partner |
| Conflicts with significant others or domestic violence | Pancreatitis | Many emergency department contacts |
| History of child abuse or neglect | Hypertension | Many physician contacts |
| Decreased job performance or chronic unemployment | Gastritis, esophagitis | Child with neonatal narcotic abstinence syndrome |
| Suicidal gestures, thoughts, or attempts | Neurologic disorders | Child with alcohol-related birth defects |
| Car accidents | Poor nutritional status | Placement of other children outside the home |
| Cited for driving while intoxicated | Hematologic disorders | Complex perinatal histories and outcomes |
| Depression | Seropositivity for HIV | Psychiatric treatment or hospital admissions |
| Irritability or agitation | Bacteremia | Affective disorders |
| Difficulty concentrating | Alcoholic myopathy | Infants with low birth weights |
| Mood swings, outbursts of anger | Sensory impairment | Frequent physician prescriptions for mood-altering drugs |
| Inappropriate behavior | Problems of sepsis, cellulitis | Family history of alcoholism or other drug dependency |
| Memory lapses and losses or blackouts | Hepatitis | Sudden infant death syndrome |
| Intoxicated behavior | Abscesses | Family dissolution |
| Smell of alcohol on breath | Mitral valve disease | |
| Unreliability or unpredictable behavior | Septicemia | |
| Missed appointments | Swelling and erythema of hands | |
| Intense daily drama, family chaos | Overdose | |
| Slurred speech | Withdrawal effects | |
| Staggering gait | Pulmonary infections | |
| | Hair loss | |
| | Erratic menses | |
| | Loss of appetite | |
| | Poor dental hygiene | |
| | Anemia | |
| | Tuberculosis | |
| | Sexually transmitted disease | |
| | Obstetric complications, including spontaneous abortion, abruptio placentae, breech presentations, previous cesarean section, eclampsia, intrauterine growth retardation, premature labor and delivery and premature rupture of membranes, intrauterine fetal death, postpartum hemorrhage | |

HIV=human immunodeficiency virus

### The CAGE Questionnaire

1. Have you ever felt you should *C*ut down on your drinking?
2. Have people *A*nnoyed you by criticizing your drinking?
3. Have you ever felt bad or *G*uilty about your drinking?
4. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (*E*ye-opener)?

**Figure 1.**—The CAGE questionnaire is used to assess the possibility of a drinking problem. A "Yes" answer to 2 or 3 out of the 4 questions strongly suggests the presence of alcoholism (from Mayfield et al[9]).

### Short Michigan Alcoholism Screening Test

1. Do you feel you are a normal drinker? (By normal we mean you drink less than or as much as most other people.) (No)
2. Does your wife, husband, a parent, or other near relative ever worry or complain about your drinking? (Yes)
3. Do you ever feel guilty about your drinking? (Yes)
4. Do friends or relatives think you are a normal drinker? (No)
5. Are you able to stop drinking when you want to? (No)
6. Have you ever attended a meeting of Alcoholics Anonymous? (Yes)
7. Has drinking ever created problems between you and your wife, husband, a parent, or other near relative? (Yes)
8. Have you ever gotten into trouble at work because of drinking? (Yes)
9. Have you ever neglected your obligations, your family, or your work for two or more days in a row because you were drinking? (Yes)
10. Have you ever gone to anyone for help about your drinking? (Yes)
11. Have you ever been in a hospital because of drinking ? (Yes)
12. Have you ever been arrested for drunken driving, driving while intoxicated, or driving under the influence of alcoholic beverages? (Yes)
13. Have you ever been arrested, even for a few hours, because of other drunken behavior? (Yes)

**Figure 2.**—The Michigan Alcoholism Screening Test is another test used to indicate the probable presence of a drinking problem. The responses in parentheses indicate the presence of alcoholism (from Selzer et al).[10]. Scoring: 0-1 point = no alcoholism, 2 points = possible alcoholism, 3 points = alcoholism

tioned that the baby's father may be addicted to cocaine and that your family has expressed concern to you.

*Step 2:* Continued cocaine use during pregnancy could be harmful to you and your baby. It has caused infants to be very small and can put them at risk to have problems in development and functioning. Some cases of fetal strokes (bleeding in the brain) have happened in babies whose mothers used cocaine; it can also cause the placenta to separate in part or completely from the wall of the uterus. If this happens, your baby is at risk to die. Cocaine also causes your blood pressure to rise, and so you are at a greater risk for heart attack and stroke. It can also cause a loss of appetite that is not good for pregnancy; you need good nutrition for a healthy pregnancy for you and your baby.

*Step 3:* I am concerned that you may have a problem with cocaine.

*Step 4:* Here is the phone number of the women's cocaine treatment program. You can talk confidentially to them about your cocaine problem. Please make an appointment to talk to them this week. After you enroll in treatment there, I would like to get your written permission to talk with them also in order to give you support for your efforts in recovery.

*Step 5:* You need to know that in this county, any baby who has a positive toxicologic urine test is reported to the child welfare services for evaluation of the mother's ability to parent. I want to advocate for you within the hospital setting, but you need to be enrolled in prenatal care consistently throughout your pregnancy and to become a client at the cocaine treatment program with open communication to me. If you do both of these things, I will support you and advocate for you in any way I can at the time of the birth of your baby and during the postpartum period. You can get help for this problem; recovery is possible, and you can learn to live comfortably without the use of drugs.

Because denial is a basic component of the disease of addiction, the physician may expect to encounter at least

| *Drug and Alcohol Use* | *Year of First Use* | *Use This Year* | *Use This Month* | *Frequency of Use This Month* | *Maximum Tolerance* |
|---|---|---|---|---|---|
| Wine | | | | | |
| Beer | | | | | |
| Liquor | | | | | |
| Tobacco | | | | | |
| Marijuana | | | | | |
| Caffeine | | | | | |
| Phenylcyclidine piperidine (PCP) | | | | | |
| Cocaine | | | | | |
| Tranquilizers* | | | | | |
| Opiates† | | | | | |
| Chemical exposures‡ | | | | | |
| Other hallucinogens§ | | | | | |
| Other stimulants‖ | | | | | |
| Other¶ | | | | | |

*Tranquilizers: diazepam (Valium), amitriptyline hydrochloride (Elavil), methaqualone (Ouaalude; sedative-hypnotic), trifluoperazine hydrochlorioe (Stelazine), chlorpromazine hydrochloride (Thorazine), thioridazine hydrochloride (Mellaril), fluphenazine hydrochloride (Prolixin), thiothixene (Navane), doxepin hydrochloride (Sinequan), barbiturates such as Seconal (secobarbital) and Tuinal (amobarbital sodium and secobarbital sodium).

†Opiates: heroin, methadone hydrochloride, morphine sulfate, meperidine hydrochloride (Oemerol), aspirin-oxycodone hydrochloride (Percodan), codeine, propoxyphene napsylate (Oarvon, Oarvocet), hydromorphone hydrochloride (Oilaudid).

‡Chemical exposures: paints, insecticides, lead, varnish, solvents, and the like.

§Hallucinogens: LSO, PCP, dimethyltryptamine (OMT), mushrooms, mescaline, methylenedioxymethamphetamine (MOMA, "ecstasy").

‖Stimulants: cocaine, methamphetamine ("speed," "crystal"), methylphenidate hydrochloride (Ritalin), diet pills, dextromethamphetamine sulfate (Oexedrine, Oexamyl).

¶Over-the-counter medications: aspirin, acetaminophen (Tylenol, Oatril), Nyquil (a combination of pseudoephedrine hydrochloride, doxylamine succinate, dextromethorphan hydrobromate, and acetaminophen), diphenhydramine hydrochloride (Sominex); other medications purchased in drugstore or supermarket with a prescription; vitamins.

**Figure 3.**—This screening questionnaire may be given to a patient during the intake process to assess possible drug or alcohol use (from Ruggiero and Jessup, unpublished data, 1987).

some denial. This behavior on the part of the patient should not, however, deter the physician from continuing the intervention and making the appropriate referral. When, in Step 1, the physician states the indicators of a problem, this must be done in as explicit detail as possible. This has a particular effect on the denial process of the patient because it makes it more difficult for the patient to completely deny the existence of a problem. The expression of concern should be given in a genuine manner with the extension of hope for recovery, as this may be instrumental in the woman's decision to seek treatment. It is therapeutic to place discussions of treatment and recovery in the context of something that gives benefit to the woman and her infant, rather than something that is a sacrifice. The issue of focusing on the self is one that arises for a chemically dependent woman in recovery.[10] Therefore, it is better to say something like, "Treatment will help you to feel better physically and emotionally, and you will have a better chance of having a healthy baby," rather than, "Do it for the baby." Language that provokes guilt should be avoided during the intervention process as those feelings of guilt may bar a woman from seeking treatment.

It is hoped that through the intervention process a pregnant woman with a drug or alcohol addiction will be compelled to take the treatment option. No intervention should be considered a failure even if the woman does not seek treatment for her addiction. Each time that the conspiracy of silence is broken, the wall of denial drops a bit further.

Intervention can be a powerful tool to facilitate recovery. If a chemically dependent pregnant woman does not seek treatment after the intervention is completed and continually does not comply with the course of prenatal care or drug or alcohol treatment, other ethical dilemmas present for the physician, and other courses of action may be indicated.

## Dealing With Noncompliance

Noncompliance in prenatal care and chemical dependence treatment is particularly disturbing to many health professionals, including physicians, because it potentially affects the developing fetus as well as the woman herself. Surely a woman, once she becomes pregnant, has moral and ethical responsibilities to do everything she can to have a healthy pregnancy and infant. Yet, if that responsibility of the woman is legally mandated by the state, "such a policy would impose an unprecedented system of surveillance and coercion oppressive to all women of childbearing age" (Judith Rosen, JD, Legal Counsel, California Advocates for Pregnant Women, "Chemically Dependent Pregnant Women and Drug-Exposed Infants: Legal Issues and Implications," California Advocates for Pregnant Women, unpublished manuscript, 1989). Safe, confidential treatment options that meet the extensive needs of this population must be available and referral made before any legal, coercive, or prosecution-oriented strategies are carried out.

One issue under question regarding noncompliance in this population is the possibility of a dual diagnosis—that is, primary psychopathology (occurring first) and secondary chemical dependence (occurring later). If a woman has never received treatment for a primary psychiatric illness, she may be greatly at risk for continued drug or alcohol use.[11(p8)] It has been estimated that 10% to 15% of women with alcoholism have a primary affective disorder predating the beginning of their chemical dependence.[21] It has also been noted that some women with bipolar illness (manic depressive disorders) are more likely to be admitted to a psychiatric hospital and have increased morbidity of their disorder with excessive drinking.[12] If noncompliance continues, the physician should strongly consider consultation with and evaluation of the patient by a psychiatrist with a clinical knowledge of addiction medicine. In the addiction-only population of pregnant women, drug therapy is not indicated. For the dual-diagnosis group, it may be indicated, in which case it would need to be applied under the rubric of the benefit-to-risk ratio. In addition, psychotherapy with the goal of long-term insight for an addicted or alcoholic person may be helpful after an initial period of abstinence, recovery, and attention to those as the primary focus. For a patient with a dual diagnosis, psychotherapy in concert with recovery efforts is the optimum mode of treatment. An addicted woman who has had more than one infant affected by drugs and alcohol may well have a dual diagnosis; moreover, she may never have been evaluated, never treated, and perhaps even prosecuted for her dual diseases and the resultant behavior.

Assuming all diagnostic and treatment bases are covered and the patient still remains noncompliant, it is appropriate, after the birth of the child, to make a referral to the child welfare services of the resident county of the patient. Welfare service workers will then evaluate the risk to the child and make appropriate recommendations regarding the disposition of the child and requirements the mother must fulfill. Continued custody of the child may be contingent on the fulfillment of and compliance with a service plan set forth by the child protection agency.[13] Such a plan may include the following:

- Participation in a chemical dependence treatment program on an ongoing basis,
- Visits by a public health nurse for infant and family evaluation,
- Regular and ongoing pediatric care,
- Individual or family therapy as indicated, and
- Regular meetings with child protective services personnel.

It is appropriate for the primary care physician to provide information for the development of the service plan if child welfare services are to be involved in the case at all. Observation and advocacy for the woman and her infant are critical at this juncture.

The observations of the physician, including documentation of all attempts to intervene, are critical to the child welfare services evaluation of the case. Referral to these services before the birth of the infant is not mandatory in most states as the fetus is not covered under the mandate of the law relative to child abuse and neglect reporting (J. Rosen, unpublished data, 1989). Local jurisdiction will determine how physicians shall act; many counties in California do require reporting to child welfare services at the birth of an infant who has a positive toxicologic screening test.[3]

Physicians must guard against subjective measures of addiction criteria that may be based on stereotypic thinking and outdated belief systems. Most appropriate, a physician should have protocols for making the referral to child welfare services or for even ordering urine toxicologic testing. Some criteria for reporting to child welfare services are based in part on observation for psychosocial risk factors that are objectively noted and not dependent on race or socioeconomic status.[14] Prenatal noncompliance may result in a threatened

or actual loss of custody of the child. In some cases, this may be therapeutic as the addicted or alcoholic mother will have the opportunity to face some negative consequences of her disease; it may be her experience of "hitting bottom" in this way that moves her to seek treatment. In any case, the offering of treatment of the addiction should always be the first response of the health care system and the primary physician.

## Toxicologic Screening

Urine toxicologic testing is certainly a part of the diagnostic process; yet, an overreliance on this technology can be misleading and incomplete. The debate over informed consent for such testing has recently intensified, and that debate has moved into perinatal medicine as well.[3] According to Smith,

> Traditionally, testing of a biological fluid was for the purpose of diagnosis and initiating a treatment plan . . . . [W]omen are generally not given informed consent for testing biological fluids for the release of the results to law enforcement. This, of course, is counter to the public health model . . . compromising the doctor-patient relationship" (Calif Advocates for Pregnant Women Newsletter, July-August 1989).

Legal experts in the area of addiction medicine advocate that urine testing of pregnant women should become a consensual procedure so that informed consent is obtained at the time of the initiation of any treatment that includes toxicology screening (L. Nelson, JD, oral communication, November 1989; Westley Clark, MD, JD, oral communication, October 1989). Support for this approach is growing among advocates for pregnant chemically dependent women as well (N. St Clair, MS, oral communication, July 1989). The premise of informed consent has also become increasingly accepted as a basic principle in the ethical practice of medicine.

> According to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Medicine,[15] informed consent as the ethical basis of patient care serves two purposes: it places respect for a patient's self-determination at the center of the physician-patient relationship and it recognizes that an active patient role in treatment decisions is often the best guarantee that these decisions will in fact promote patient well-being.[16]

Experts in perinatal medicine have urged physicians to make toxicologic screening a routine part of each prenatal visit,[14] but the costs incurred and the logistics of such a recommendation make this impractical for many practitioners. A single urine test also only gives a "snapshot" of a patient's drug use on a particular occasion at one point in time. This is akin to drawing one blood specimen from a pregnant woman with diabetes mellitus and concluding the diagnosis. Laboratory error is also a fact of life for most toxicologic screening; though false-positives are rare, they do occur. False-negatives also present a problem for practitioners; an overreliance on urine testing may cause the physician to miss the diagnosis of addiction. Rather, a working, in-depth knowledge of the disease of addiction and the ability to conduct a meaningful verbal interview are paramount in any workup for addiction. Though toxicologic screening is a valuable part of the assessment of a patient and invaluable indeed for the neonatologist, it cannot measure a patient's motivation for treatment, the chronicity of her disease, nor her willingness to seek recovery. Any evaluation of addictive disease must include those variables.

## Interdisciplinary Case Management

A pregnant addicted or alcoholic woman interacts with many different providers during and after her pregnancy. In most communities, the services available are not comprehensive and, even when offered, are usually delivered in a fragmented way with little or no communication among the players. The traditional "treatment plan" for a pregnant addict in communities where services do not exist generally consists of whatever the woman has pulled together for herself and been able to participate in.

Ideally, physicians will have resources available for referral to drug treatment; childbirth education; parenting classes; voluntary and anonymous human immunodeficiency virus testing, counseling, and social services; family planning and pediatric care; and the 12-step programs of Alcoholics Anonymous and Narcotics Anonymous. To maximize outcomes for a woman and her infant, however, case management is definitely indicated. Physicians are in an ideal position to facilitate open communication and planning among all the providers of services to a pregnant chemically dependent woman. All providers should be in regular contact to assure that all facts are known, that services do not overlap, and that "splitting" of the treatment team by the patient is minimized. A treatment planning meeting is the most appropriate method to achieve these goals. Of any of the multitude of complex medical conditions, perinatal addiction especially requires a team effort.[17(p13)]

## Physicians as Advocates—Policy and Community Standards

The debate on the criminalization of drug use during pregnancy is currently raging. Those who wish to criminalize maternal drug addiction and alcoholism have advocated enforcing mandatory jail sentences and incarceration in "custodial settings" for the duration of a pregnancy.[18] As a means of prosecuting pregnant addicts, others have sought to alter the child abuse statute in California to include the fetus.[19] The legal and ethical issues surrounding pregnancy and addiction are also intimately connected to the current erosion of women's reproductive rights as shown by the Webster case heard in the United States Supreme Court in July 1989.[22]

It is assumed that most providers of services to pregnant women with drug or alcohol abuse share the following goals: to reduce the prevalence of the acquired immunodeficiency syndrome in the perinatal population, to reduce the incidence of alcohol- and drug-related birth defects, to prevent child abuse and neglect, and to facilitate recovery for chemically dependent women and their families. Yet, many of the cases that have been litigated in California are those wherein a health professional figured prominently as the reporter of the case to criminal justice authorities. It may be out of desperation, the fear of a malpractice suit, or the physician's own unresolved emotions about addiction that the traditional role of healer has, in some cases, shifted to that of a law enforcement agent. Yet, if physicians wish to accomplish these goals in their work with the addicted perinatal population, a solid position of noncriminalization and advocacy for treatment and affordable prenatal care seems eminently the preferred approach.

In each case in California wherein a pregnant addict has been prosecuted, it has been in communities lacking a strong, proactive position on the right of pregnant addicts and alcoholics to treatment. Current events and public sentiment now demand that all health professionals forge a policy that supports treatment and reinforces the traditional role of health professionals as healers and helpers. Lacking policy in this

area, law enforcement becomes the policy and the procedure. Community standards of practice that address medical management, chemical dependence treatment, and legal and ethical issues must now emerge lest these be left to the criminal justice system to merely adjudicate. Physicians are in a pivotal role to facilitate the return of a public health model of treating addiction and alcoholism in pregnant women that is inclusive in scope and comprehensive in nature.

### REFERENCES


1. Smith DE, Milkman HB, Sunderwirth SG: Addictive disease: Concept and controversy. *In* Milkman HB, Shaffer HJ (Eds): The Addictions: Multidisciplinary Perspectives and Treatments. Lexington, Mass, Lexington Books, 1985

2. Reed BG: Developing women-sensitive drug dependence treatment services: Why so difficult? J Psychoactive Drugs 1987; 19:151-164

3. Health and Human Services Committee and Senate Select Committee on Children and Youth: Joint hearing on Impact of Substance-Exposed Infants on Child Welfare Services, Los Angeles, October 20, 1989

4. Beschner GM, Reed BG, Mondanaro J (Eds): Treatment Services for Drug Dependent Women, Vol 1. Rockville, Md, US Dept of Health and Human Services (DHHS), National Institute on Drug Abuse, 1981

5. Finnegan LP: Drug Dependence in Pregnancy: Clinical Management of Mother and Child, US DHEW publication No. (ADM) 79-678. Rockville, Md, US Dept of Health, Education and Welfare, National Institute on Drug Abuse, 1979, pp 46-47

6. Mondanaro J, Reed B: Current Issues in the Treatment of Chemically Dependent Women. Rockville, Md, US DHHS, National Institute on Drug Abuse, 1987

7. Rosett HL, Weiner L, Edelin KC: Treatment experience with pregnant problem drinkers. JAMA 1983; 249:2029-2033

8. Michigan Alcoholism Screening Test. Am J Psychiatry 1971; 127:1653-1654

9. Mayfield D, McLeod G, Hall P: The CAGE questionnaire: Validation of a new alcoholism screening instrument. Am J Psychiatry 1974; 131:1121-1123

10. Selzer M, Vinokur A, van Rooijen L: A self-administered short Michigan Alcoholism Screening Test. J Stud Alcohol 1975; 36:117-126

11. Bissel C: Introduction, *In* Rachel V: A Woman Like You: Life Stories of Women Recovering From Alcoholism & Addiction. San Francisco, Harper & Row, 1985

12. Meyer R: Psychopathology and Addictive Disorders. New York, Guilford Press, 1986

13. Reich LH, Davies RK, Himmelhoch JM: Excessive alcohol use in manic-depressive illness. Am J Psychiatry 1974; 131:83-86

14. Issue 602, No. 83-76; 30-324 Services Plan (manual letter). Sacramento, California Dept of Social Services, 1983

15. Chasnoff IJ: Drugs, Alcohol, Pregnancy and Parenting. Hingham, Mass, Kluwer Academic Publishers, 1988, pp 197-200

16. President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research: Making Health Care Decisions, vol 1. Washington, DC, Government Printing Office, 1982

17. Forrow L, Wartman SA, Brock DW: Science, ethics, and the making of clinical decisions—Implications for risk factor intervention. JAMA 1988; 259:3161-3167

18. Daghestani A: Psychosocial characteristics of pregnant women addicts in treatment. *In* Chasnoff IJ (Ed): Drugs, Alcohol, Pregnancy and Parenting. Hingham, Mass. Kluwer Academic Publishers, 1988, pp 7-16

19. Wilson P: Child Abuse During Pregnancy Prevention Act of 1989. Congressional Record, August 1, 1989; §9319

20. Royce R: Senate Bill 1070 (proposed and defeated). California State Senate, 1987

21. Schuckit M, Pitts FN Jr, Reich T, et al: Alcoholism 1—1: Two types of alcoholism in women. Arch Gen Psychiatry 1969; 20:301-306

22. Webster v Reproductive Health Services, 109 SCt 3040 (1989) (No. 88-605)

**Addiction Medicine**
**and the Primary Care Physician**

# Drug-Exposed Neonates

GEORGEANNE HOEGERMAN, MD; CATHERINE A. WILSON, MEd; ELLEN THURMOND, LCSW; *and*
SIDNEY H. SCHNOLL, MD, PhD, *Richmond, Virginia*

*Drug use during pregnancy can have detrimental effects—both nonspecific and highly specific—on the perinatal outcome. Nonspecific effects include fetal growth retardation, resulting in small infants and decreased head circumference. Specific effects include facial dysmorphology and organ system anomalies such as alcohol-related birth defects. Patients abusing drugs are at an increased risk for preterm labor, thereby placing an already compromised fetus at increased risk. The number of mothers and infants being infected by the human immunodeficiency virus from sharing needles, multiple sexual contacts, and mother-to-infant transmission is increasing at an alarming rate.*

(Hoegerman G, Wilson CA, Thurmond E, et al: Drug-exposed neonates, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:559-564)

Recent reports on the prevalence of drug use during pregnancy in an urban population indicate that as many as 17% of women have used cocaine, 28% have used marijuana, 44% smoked cigarettes, 59% consumed alcohol, and 4% used opiates.[1] It is thought, however, that self-disclosure alone misses a considerable fraction of substance-abusing pregnant women. Most studies of drug use during pregnancy have focused on hospital-based populations. Non-hospital-based physicians need to look at the substance misuse and abuse of their pregnant patients. In this article the abusable drugs we focus on that affect the neonatal outcome are opiates, alcohol, stimulants such as amphetamines and cocaine, hallucinogens, marijuana, nicotine, and others. In addition to the use of illicit drugs, patients tend to misuse legally available drugs. Over-the-counter drugs such as alcohol and nicotine are among the most teratogenic agents and are associated with substantially increased neonatal morbidity and mortality.[2-4] Clearly, a wider recognition of this problem is necessary to reduce the prenatal and postnatal problems associated with drug use during pregnancy.

## Perinatal Pharmacology

The study of the pharmacology of drugs during pregnancy is at best extremely difficult. Confounding variables such as multiple drug use, the unreliability of self-reporting, and an inability to conduct experimental research on fetuses leads to a paucity of human data. Studies of animals are difficult to extrapolate to humans because there is extensive evidence indicating that the effects of drugs on fetal development in animals may not relate to the effects of the same drugs in humans.[5-7]

Despite these problems, some principles are established:

- The time during pregnancy that a drug is taken is extremely critical. The first eight weeks of pregnancy—often before a woman knows she is pregnant—are usually the most critical in terms of embryonic development.
- Placental function is important in predicting drug effects because the placenta is not a passive, sievelike structure but an active organ with many metabolic functions. Recent studies have indicated that the placenta is able to produce enzymes involved in oxidation, reduction, hydrolysis, and conjugation of drugs. All drugs are able to cross the placenta to some extent, especially if given in large quantities over a prolonged period. A simple rule of thumb is that any drug that crosses the blood-brain barrier and has an effect on the central nervous system of the mother will also cross the placenta.
- Maternal factors associated with pregnancy can alter drug levels. Hormonal changes, alterations in plasma proteins, shifts in the body water:fat ratio, and changes in gastrointestinal motility all alter drug pharmacokinetics and dynamics.
- Fetal exposure to drugs may have significant effects on the newborn and on later life.

Little is known about the long-term effects of fetal drug exposure on development, intellectual capabilities, learning behavior, physical effects, and later responses to drugs including susceptibility to addiction in adolescence and adult life.

## Teratogenic Effects of Drugs of Abuse

A teratogen is any substance that alters the structure or function of the developing fetus, placing it in a compromised state. The teratogenic effects of abused drugs include dysmorphic, behavioral, and neurobiochemical changes.

Theoretically, the development of a teratogenic effect is dependent on several variables that coalesce in an interactive way, resulting in fetal abnormalities. These variables are enumerated in Table 1. One agent may have a myriad of teratogenic effects, each of which is expressed independently. For example, the threshold level for damage may differ for the types of effects. Modest ingestion of a drug such as alcohol

From the Departments of Medicine (Hoegerman and Schnoll) and Psychiatry (Schnoll) and the Division of Substance Abuse Medicine (Wilson and Thurmond), Medical College of Virginia Hospitals, Virginia Commonwealth University, Richmond.

This work was supported in part by funds from the Commonwealth of Virginia Center on Drug Abuse.

Reprint requests to Georgeanne Hoegerman, MD, Division of Substance Abuse Medicine, Box 109 MCV Station, Richmond, VA 23298-0109.

ABBREVIATIONS USED IN TEXT

HIV = human immunodeficiency virus
IV = intravenous
SIDS = sudden infant death syndrome

may not put a fetus at risk for dysmorphic effects such as craniofacial anomalies, yet seriously compromises subtler areas such as behavior.[4,5]

As we learn more about teratogenicity, it is apparent that some teratogenic effects of drugs may have been missed in earlier studies. Recent evidence points to a higher frequency of alcohol-related birth defects when screening is done in early childhood as opposed to at birth.[3] Newborn screening will tend to underrepresent behavioral effects, as these may only become observable over time.

*Problems Assigning Specific Effects to a Particular Drug*

Table 2 lists the commonly reported teratogenic effects of abused drugs. It is difficult to determine the cause of a specific teratogenic effect. The frequency of teratogenicity may be low, requiring a large number of pregnant addicts to establish a specific effect. In addition, there are few "pure" opiate addicts or "pure" alcoholics, and the confounding effects of nutrition, genetic susceptibility, and environmental factors make it difficult to ascribe effects to a specific drug. Another variable is the impurity of street drugs. Because of widespread contamination and substitution, it is difficult to determine from the history exactly what a patient has taken. The contaminating drugs could be a more serious threat to health than the drug the person thought she was buying. Those materials may be teratogenic in their own right or result in interactions having teratogenic potential.[6] Information provided by the patient should be verified by urine toxicology. Physicians should not feel obligated to obtain any special consent from pregnant patients for doing urine toxicology beyond their usual, general consent for diagnosis and treatment. The diagnosis and clarification of the use of abusable drugs in the clinical setting are clearly appropriate and mandated tasks of all health care professionals caring for a pregnant woman and fetus.[7,8]

TABLE 1.—*Variables Affecting Teratogenic Outcome*

| |
|---|
| Threshold at which the particular effect occurs (dose and duration) |
| Fetal susceptibility (genetic vulnerability) |
| Timing of exposure |
| Pharmacology of the drug |
| Maternal factors—age, nutrition, hormonal, and uterine environment |
| Coexistence of infections such as rubella or the acquired immunodeficiency syndrome |
| Confounding effects of other abused drugs such as nicotine |
| Environmental factors—socioeconomic status, climate, and altitude |

*Behavioral and Neurobiochemical Teratogenesis*

The development of neonatal behavioral assessment scales has helped to delineate behavioral teratology.[9-11] At present there is little understanding of the etiology and pathogenesis of these behavioral changes. They may be related to alterations in brain development from drug exposure at any time during pregnancy. These effects may also be due to postnatal exposure of immaturely functioning organs, delaying excretion of various drugs.[7] Studies have shown that diazepam administered during labor in a single dose takes from 10 to 18 days to be excreted by the neonate. Meperidine hydrochloride is excreted over five to seven days, and recent studies have shown that cocaine takes three to five days to be excreted by neonates. These slow excretion times for drugs can result in prolonged drug effects, with withdrawal syndromes occurring weeks to months after birth. This may interfere with behavioral assessment. Withdrawal syndromes may also affect brain development in neonates.

It is therefore critical to distinguish signs of neonatal intoxication or withdrawal from other causes of behavioral changes. In addition, parent-child interactions and nutritional and environmental factors may affect behavior. All drugs of abuse have been shown to correlate with behavioral changes in the neonate. On the Brazelton Neonatal Behavioral Assessment Scale, impairments in interactive abilities, motor maturity, and organizational responses to environmental stimuli (state changes) have been described.[6,9-12] These infants are frequently difficult to nurture because of the behavioral changes resulting in poor mother-infant bonding. In fact, the behavioral consequences on maternal-child bonding may be the most pervasive and devastating legacy of perinatal addiction.

*Fetal Growth*

The most obvious effect of drug exposure during pregnancy is generalized growth retardation and a small head circumference. It occurs in newborns with exposure to nicotine, opiates, alcohol, or cocaine.[2,9-11,13,14] This may be due in part to inadequate nutrition during gestation in the addicted population as well as direct effects of the drug impeding normal development. Isolated cases of a failure to catch up in growth and a failure to thrive have been reported, although larger, prospective studies have not substantiated these reports.[3]

*Sudden Infant Death Syndrome*

The frequency of the sudden infant death syndrome (SIDS) is increased in infants born to addicts. Chasnoff and

TABLE 2.—*Commonly Reported Teratogenic Effects of Abused Drugs*

| *Specific Fetal Effects* | *Opiates* | *Alcohol* | *Other Sedative-Hypnotic Drugs* | *Cocaine* | *Other Stimulants* | *Hallucinogens* | *Marijuana* | *Nicotine* |
|---|---|---|---|---|---|---|---|---|
| Structural nonspecific growth retardation | X | X | ... | X | ... | ... | X | X |
| Specific dysmorphic effects | ... | X | ... | X | ... | ... | ... | ... |
| Behavioral | X | X | X | X | X | X | X | X |
| Neurobiochemical (abstinence syndrome) | X | X | X | ... | ... | ... | ... | ... |
| Increased fetal and perinatal mortality | X | X | ... | X | ... | ... | ... | X |
| Women reporting use in pregnancy (varies with population),% | 5 | >50 | <5 | ≤20 | <5 | <5 | 5-34 | >50 |

co-workers found a 15% incidence of SIDS in infants with exposure to cocaine in utero as opposed to a 4% incidence from exposure to opiates, both significantly increased over that of non-drug-abuse cases.[15] Nicotine exposure in utero also increases the frequency of apnea.[2] Other investigators have not been able to substantiate these findings.[16] More studies are needed to determine why these differences occur.

*Specific Drug Effects*

*Alcohol.* Alcohol-related birth defects are the best-defined teratogenic effects. They include structural, behavioral, and neurobiochemical changes, which are enumerated in Table 3.[3-7,13,17] Common structural facial features are depicted in Figure 1.[4]

*Cocaine.* An increased incidence of genitourinary malformations including the prune-belly syndrome, gastrointestinal anomalies (ileal atresia), and central nervous system effects (intracranial hemorrhage) have been described with cocaine use.[17-24] These are thought to be due to cocaine's vasoconstrictive properties. More research is needed to determine if these are truly cocaine-specific effects.

*Nicotine.* Cigarette smoking is a pervasive finding in substance abusers. Much of the morbidity commonly attributed to abused drugs may in fact be due to nicotine. The perinatal death rate is 34% higher in infants of smoking mothers.[2,25] Central apnea is increased in these infants.[2] Pronounced fetal growth retardation, prematurity, and later respiratory tract infections are all well described in infants of smokers.[6]

*Opiates.* No specific effects other than what has been described for generalized drug abuse have been established for opiates.

## Management During Pregnancy

Because the use of street drugs is associated with repeated episodes of intoxication, withdrawal, and exposure to street-drug contaminants, one of the approaches to treatment of a chemically dependent pregnant woman is to place her on an alternative drug regimen with the hope that it will reduce the street-drug use. The only drug available to treat addicted pregnant women at the present time is methadone hydrochloride, which is used in the treatment of opiate dependence. Methadone is useful because it is long acting, and therefore a woman is able to maintain fairly consistent blood levels in contrast to using opiates on the street that are usually short acting, resulting in wide swings in blood levels. These rapid swings from intoxication to withdrawal can have severe adverse effects on the fetus, often producing premature labor and spontaneous abortions. Methadone also reduces the use of street opiates and other drugs by blocking withdrawal and craving. Street heroin is frequently "cut" with substances such as quinine or procaine, which can have teratogenic effects.

Experience has shown that a methadone dose of less than 20 mg per day at the time of delivery substantially reduces the presence of neonatal withdrawal signs and symptoms.[7] Every effort should be made to place a patient on an effective dose of methadone to reduce continued street-drug use and eliminate signs of withdrawal. Bear in mind that blood concentrations of methadone can fall precipitously late in gestation due to metabolic effects. Splitting the daily dose of methadone may help to avoid having to increase it to maintain a uniform blood level.[7]

Despite the widespread use of alcohol, sedative-hypnotic agents, and stimulants during pregnancy, there are no maintenance drugs currently accepted for the treatment of women dependent on these substances. Phenobarbital and benzodiazepines have been used to withdraw women who have abused alcohol and sedative-hypnotic drugs during pregnancy, but there are no studies documenting the effects of these drugs on withdrawal and long-term consequences. We use an inpatient pentobarbital challenge test to determine the initial dose of phenobarbital. Our withdrawal protocol is detailed in Table 4. Other drugs such as methadone are tapered by a gradual reduction of the dose at a rate of from 5% to 10% per day of the initial dose. This information is based on clinical experience in our own program and case reports. There are no studies that have carefully assessed withdrawal

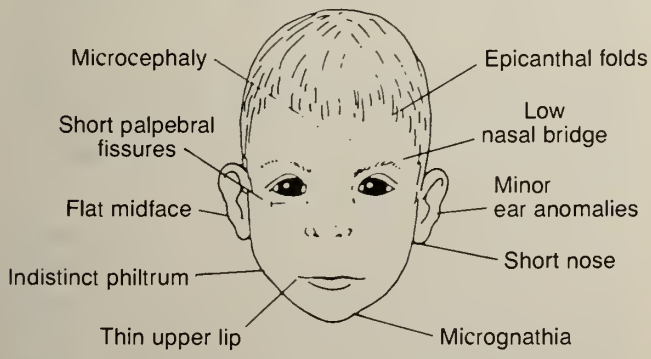



**Figure 1.**—The figure shows the typical facial features found in the fetal alcohol syndrome. The features on the left are those that are the most characteristic and delineating; those on the right are less frequently observed and are not as differentiating (from Streissguth et al).[4]

TABLE 3.—*Alcohol-Related Birth Defects*

| |
|---|
| Structural changes |
| Prenatal growth retardation |
| Microcephaly |
| Short palpebral fissure |
| Indistinct philtrum |
| Hypoplastic maxilla and flattened midface |
| Thin vermillion border |
| Cardiac defects |
| Behavioral changes |
| Mild to moderate mental retardation |
| Delayed motor and language |
| Increased irritability |
| Decreased ability to habituate |
| Neurobiochemical changes |
| Neonatal abstinence syndrome |

TABLE 4.—*Inpatient Protocol for Withdrawal From Alcohol, Sedative-Hypnotic Drugs, or Both*

| *Step* | *Procedure* |
|---|---|
| 1 | Give 200 mg pentobarbital sodium orally and wait 1 hour |
| 2 | Look for signs of intoxication: nystagmus, ataxia, drowsiness, decreased pulse and blood pressure |
| 3 | If signs of intoxication present, stop test *or* If signs not present, give pentobarbital, 100 mg orally every hour until intoxication or until a total of 600 mg has been given |
| 4 | Convert to phenobarbital, 30 mg for every 100 mg of pentobarbital that was given |
| 5 | Decrease phenobarbital dose by 10% of initial dose over the next 10 days |

phenomena in women who are dependent on drugs. Withdrawal during pregnancy under medical supervision is thought to lessen the stress and adverse consequences on the fetus, but well-controlled studies to substantiate this have not been done.

Once a pregnant woman is known to be chemically addicted, it is imperative that issues relating to her substance abuse be identified and addressed. Intervention at such a critical time may avoid societal sequelae including infant abandonment, inflated medical costs, special educational problems, and the intragenerational transmission of substance abuse. There is increasing awareness of the cost of ignoring substance-abusing mothers for society in terms of infant outcome.

## Evaluating a Newborn

Perinatal addiction puts an infant at risk for immediate as well as long-term problems. An appropriate diagnosis of perinatal drug exposure is imperative. The clinician should consider toxicologic screening at delivery if there is any suggestion of drug use either before or during the pregnancy. A mother's inability to abstain from drug use during pregnancy when it clearly jeopardizes her unborn child is pathognomonic of addiction.

In women using drugs in pregnancy, the rates of meconium staining, fetal monitor abnormalities, precipitous delivery, abruptio placentae, and premature delivery are all increased.[7] These women should be observed for signs of infection because there is an increased incidence of sexually transmitted diseases and hepatitis.[7]

The infant should be evaluated for dysmorphic features specific for certain drugs such as alcohol-related birth defects or cocaine effects. Weight, height, and head circumference measurements with comparisons with norms should be done promptly. Obviously, personnel need to be alerted for signs of the neonatal abstinence syndrome.

Postnatal medical surveillance should be increased. These high-risk infants should be monitored for delayed effects into mid-childhood. Infants are at high risk from the direct teratogenic effect of the drugs as well as the effect of compromised parenting and bonding, environmental and nutritional factors, and underlying genetic factors.

## Treatment of the Neonatal Abstinence Syndrome

More than half of babies born to women with street drug or alcohol dependence will show signs of the neonatal abstinence syndrome. This nonspecific disorder is generally evident within three to five days of the mother's last use of a dependence-producing drug. Unfortunately, it is common for addicted mothers to be discharged within 36 hours of delivery.

The neonatal abstinence syndrome includes neurologic signs (tremors, hyperreflexia, and irritability), autonomic system dysfunction (yawning, sneezing, low-grade fever, and skin mottling), gut abnormalities (diarrhea, vomiting, poor feeding, and failure to thrive), and respiratory abnormalities (increased apnea). A neonatal abstinence scoring system has been developed by Finnegan.[26] This straightforward approach allows hospital personnel to objectively monitor high-risk newborns for withdrawal symptoms.

The most commonly used pharmacologic approach to a neonate with the abstinence syndrome is to administer phenobarbital.[27] A dose of 2 to 4 mg per kg of body weight given orally or intramuscularly every eight hours is recommended. We find methadone an excellent agent for treating opiate withdrawal of newborns at our institution, initially offering 1 to 2 mg of methadone twice a day. If the mother is being maintained on methadone therapy, we support her decision to nurse her infant, as opiates are passed through breast milk, preventing neonatal withdrawal. Paregoric can also be used in opiate withdrawal, with an initial dose of 0.1 to 0.5 ml per kg every four hours. Diazepam has been used by some physicians in a dosage of 1 to 2 mg twice a day in opiate-addicted newborns. We recommend tapering whatever agent is used by 10% to 20% per day. Special attention needs to be given by nursing personnel to nurturing the fragile mother-child pair during this stressful time.

## Breast-Feeding

Two thirds of American women breast-feed at hospital discharge. Because of the prevalence of drug abuse in our society, many women nurse despite continued drug ingestion. Drugs of abuse that are contraindicated during breast-feeding include amphetamines, cocaine, heroin, marijuana, nicotine (smoking), and phencyclidine.[28-30]

Drugs that should be used cautiously if a woman is breast-feeding include phenobarbital and the benzodiazepines. It is recommended that drug exposure to the nursing infant can be minimized by having the mother take the medication just after completing nursing or just before an anticipated lengthy sleep period.

Methadone use is thought to be compatible with breast-feeding if the mother receives no more than 20 mg per 24 hours. The use of other commonly prescribed opiates such as codeine and morphine is also considered compatible with nursing if used judiciously.

Although modest alcohol and caffeine consumption is currently thought to be compatible with breast-feeding, maternal alcohol ingestion of 1 gram per kg daily is thought to decrease the milk ejection reflex. A recent report underscores the controversy over the safety of nursing mothers ingesting alcohol. Little and colleagues concluded there is a dose-response relationship between alcohol consumed by nursing mothers and motor development in infants even after controlling for 100 potentially confounding variables.[31] More research is needed in this area. The best approach, however, is to discourage all drug and alcohol use by a breast-feeding woman.

## Long-term Consequences of Perinatal Addiction

Information on the long-term consequences of in utero exposure to drugs is scarce, often contradictory, and inconclusive. A confounding variable is the unstable environment in which these children are raised. It is difficult to be certain that developmental deficits or learning disabilities are caused by a drug's teratogenic effect as opposed to the consequences of an unstable, impoverished environment.

Increased neurologic abnormalities have been identified in several studies, including muscle tone discrepancies, articulation disorders, and weak visual, motor, and perceptual skills. The use of the Bayley developmental scale has yielded conflicting results among studies.[12,32-34] Chasnoff and associates found no differences between drug and non-drug-exposed infants' scores on the Bayley.[8] Bernstein and coworkers found significant discrepancies between 4-month-old infants with exposure to methadone and those with no

TABLE 5.—*Components of a Multidisciplinary Perinatal Team Focused on Substance Abuse*

| | Specialty or Discipline | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Type of Intervention* | *Obstetrics* | *Pediatrics* | *Develop Psychologist* | *Nursing* | *Social Worker* | *Occup Therapist* | *Psychiatrist* | *Rehab Counselor* | *Child Care Worker* | *Volunteer* |
| Maternal/child medical care | X | X | ... | X | ... | ... | ... | ... | ... | ... |
| Maternal/child preventive medicine | X | X | ... | X | ... | ... | ... | ... | ... | ... |
| Prenatal education | X | ... | ... | X | ... | ... | ... | ... | ... | X |
| Parenting education | ... | X | X | X | ... | X | ... | ... | X | X |
| Substance abuse education | X | X | ... | X | ... | ... | ... | X | ... | X |
| Monitor parenting skills | ... | X | X | X | X | X | ... | ... | ... | X |
| Monitor child's growth and development | ... | X | X | X | X | X | ... | ... | X | ... |
| Maternal psychological assessment | ... | ... | ... | X | X | ... | X | ... | ... | ... |
| Group or individual therapy | ... | ... | ... | ... | X | ... | X | ... | ... | ... |
| Vocational training | ... | ... | ... | ... | ... | ... | ... | X | ... | ... |
| Integration with self-help groups | ... | ... | ... | X | X | X | X | ... | ... | X |
| Provide structure to monitor sobriety | X | X | X | X | X | X | X | X | X | X |

Oevelop Psychologist = developmental psychologist, Occup Therapist = occupational therapist, Rehab Counselor = rehabilitation counselor

drug exposure using the "infant behavior record" subcomponent of the Bayley developmental scale.[35,36] Subtle discrepancies are revealed within subcategories measuring cognitive development of newborns with drug exposure.[37,38] Children who have withdrawal symptoms at birth perform less well than those without exposure to drugs and those who do not have these symptoms. Lower scores have been attributed to many compounding factors, including a lack of stimulation, genetic factors, and specific drug effects.[12]

Toddlers with exposure to methadone in utero showed more disruptive, adverse, and aggressive behaviors, such as whining, yelling, teasing, and hitting as well as a tendency to be extremely active.[12] The parenting style of methadone-maintained mothers was more authoritarian and included more harsh disciplinary behaviors such as humiliation, commands, disapproval, and yelling.[12]

Infants of women abusing drugs during pregnancy appear to be at a high risk for sequelae such as attachment difficulties, behavioral problems (disorganization, unpredictability, and distractibility), and ultimately child abuse and neglect. For that reason Los Angeles has embarked on a pilot preschool program for drug-exposed children.[39] Long-term studies are needed to validate whether intervention of this sort is appropriate or needed.

Attention to identifying these high-risk infants and intervening appropriately is critical. At the Medical College of Virginia, we have a Center for Perinatal Addictions wherein the complex needs of this compromised mother-child unit are addressed. The components of such a team are listed in Table 5.

## Relationship Between Exposure to the Human Immunodeficiency Virus and Drugs in Newborns

Mother-to-child transmission of the human immunodeficiency virus (HIV) is virtually the only source of infection in infants.[40] The virus can be transmitted across the placenta early in gestation and has been isolated in fetal tissue of eight weeks' gestation.[41]

Most HIV-positive women are intravenous (IV) drug users or sexual partners of IV drug users.[40,42] A third of infants born to HIV-positive mothers will be HIV-positive themselves by 18 months of age.[43,44] In New York City currently 55% to 60% of the IV drug users are HIV-positive. This translates to 1 in 80 of the newborn population in that city being HIV-positive.[45,46] By 1991 it is estimated that 10% of the US pediatric hospital beds will be occupied by children with the acquired immunodeficiency syndrome and that that disease will be among the top five causes of death in the 1- to 4-years age group.[40]

Women abusing drugs intravenously have several major risk factors for HIV infection:

- They become infected through the sharing of contaminated needles.
- They are involved in unsafe sexual practices.
- They are more likely to select partners who are IV drug users. Between 30% and 50% of female IV drug users resort to prostitution to either support their drug habit or to trade for drugs.[47-49]

Strong evidence exists that the multidisciplinary team approach to treating drug-abusing female addicts results in a notable change in behaviors that will no doubt diminish the spread of HIV.[50]

## Conclusion

When a pregnant woman engages in the abuse of drugs, her life-style puts her and her unborn child at risk. Direct teratogenic effects of commonly abused drugs are an obvious consequence. Evidence points to a pervasive effect on behavioral development and subsequent maternal-child interactions that have long-range implications. Indirect effects due to confounding variables associated with drug use include an increased incidence of infections such as hepatitis, sexually transmitted diseases, HIV infection, poor nutrition, inadequate prenatal and postnatal care, and violence. A mother who is actively involved with her addiction may frequently place herself in dangerous situations including destructive relationships and is at a higher risk to become involved with the judicial system. Superimposed on these factors may be psychological and social problems that preceded the pregnancy. It is crucial to include, along with obstetric and pediatric care, social and emotional support and follow-up.

### REFERENCES

1. Frank DA, Zuckerman BS, Amaro H, et al: Cocaine use during pregnancy: Prevalence and correlates. Pediatrics 1988; 82:888-895

2. Toubas PL, Duke JC, McCaffree MA, et al: Effects of maternal smoking and caffeine habits on infantile apnea: A retrospective study. Pediatrics 1986; 78:159-163

3. Graham JM, Hanson JW, Darky BL, et al: Independent dysmorphology evaluations at birth and 4 years of age for children exposed to varying amounts of alcohol in utero. Pediatrics 1988; 81:772-778

4. Streissguth AP, Sampson PD, Barr HM: Neurobehavioral dose-response effects of prenatal alcohol exposure in humans from infancy to adulthood. Ann NY Acad Sci 1989; 562:145-158

5. Mills JL, Graubard BI: Is moderate drinking during pregnancy associated with an increased risk for malformations? Pediatrics 1987; 80:309-314

6. Chasnoff IJ (Ed): Drugs, Alcohol, Pregnancy and Parenting. Hingham, Mass, Kluwer Academic, 1988

7. Chasnoff IJ (Ed): Drug Use in Pregnancy: Mother and Child. Hingham, Mass, Kluwer Academic (published by MTP Press in England), 1986

8. Chasnoff IJ, Keith L, Schnoll SH: Perinatal aspects of maternal addiction. Curr Probl Obstet Gynecol Fertil 1986; 9:403-439

9. Chasnoff IJ, Burns KA, Burns WJ, et al: Prenatal drug exposure: Effects on neonatal and infant growth and development. Neurobehav Toxicol Teratol 1986; 8:357-362

10. Chasnoff IJ, Burns WJ, Schnoll SH: Perinatal addiction: The effects of maternal narcotic and nonnarcotic substance abuse on the fetus and neonate—Problems of Drug Dependence, 1983. Proceedings of the 45th Annual Scientific Meeting—The Committee on Problems of Drug Dependence, Inc. Natl Inst Drug Abuse Res Monogr Ser 1983; 49:220-226

11. Chasnoff IJ, Schnoll SH, Burns WJ, et al: Maternal nonnarcotic substance abuse during pregnancy: Effects on infant development. Neurobehav Toxicol Teratol 1984; 6:277-280

12. Bauman PS, Levine S: The development of children of drug addicts. Int J Addict 1986; 21:849-863

13. Council on Scientific Affairs: Council report on fetal effects of maternal alcohol use. JAMA 1983; 249:2517-2521

14. Day NL, Jasperse D, Richardson G, et al: Prenatal exposure to alcohol: Effect on infant growth and morphologic characteristics. Pediatrics 1989; 84:536-541

15. Chasnoff IJ, Hunt CE, Kletter R, et al: Prenatal cocaine exposure is associated with respiratory pattern abnormalities. Am J Dis Child 1989; 143:583-587

16. Bauchner H, Zuckerman B, McClain M, et al: Risk of sudden infant death syndrome among infants with in utero exposure to cocaine. J Pediatr 1988; 113:831-834

17. Ernhart CB, Sokol RJ, Ager JW, et al: New alcohol related birth defects: Assessing the risk. Ann NY Acad Sci 1989; 562:159-172

18. Chasnoff IJ, Burns KA, Burns WJ: Cocaine use in pregnancy—Perinatal morbidity and mortality. Neurotoxicol Teratol 1987; 9:291-293

19. Chasnoff IJ, Chisum GM, Kaplan WE: Maternal cocaine use and genitourinary malformations. Teratology 1988; 37:201-204

20. Chasnoff IJ, Griffith DR, MacGregor S, et al: Temporal patterns of cocaine use in pregnancy—perinatal outcome. JAMA 1989; 261:1741-1744

21. Chasnoff IJ, Bussey ME, Savich R, et al: Perinatal cerebral infarction and maternal cocaine use. J Pediatr 1986; 108:456-459

22. Hadeed AJ, Siegel SR: Maternal cocaine use during pregnancy: Effect on the newborn infant. Pediatrics 1989; 84:205-210

23. Bingol J, Fuchs M, Diaz V, et al: Teratogenicity of cocaine in humans. J Pediatr 1987; 110:93-96

24. Chasnoff IJ, Burns WJ, Schnoll SH, et al: Cocaine use in pregnancy. N Engl J Med 1985; 313:666-669

25. Weisberg E: Smoking and reproductive health. Clin Reprod Fertil 1985; 3:175-186

26. Finnegan LP: Neonatal abstinence syndrome: Assessment and pharmacotherapy. *In* Rubaltelli FF, Granati B (Eds): Neonatal Therapy: An Update. New York, Excerpta Medica, 1986, pp 122-146

27. Kandall SR, Doberczak TM, Mauer KR, et al: Opiate v CNS depressant therapy in neonatal drug abstinence syndrome. Am J Dis Child 1983; 137:378-382

28. Committee on Drugs, American Academy of Pediatrics: Transfer of drugs and other chemicals into human milk. Pediatrics 1989; 84:924-936

29. Chaney NE, Franke J, Wadlington WB: Cocaine convulsions in a breast-feeding baby. J Pediatr 1988; 112:134-135

30. Chasnoff IJ, Lewis DE, Squires L: Cocaine intoxication in a breast-fed infant. Pediatrics 1987; 80:836-838

31. Little RE, Anderson KW, Ervin CH, et al: Maternal alcohol use during breast-feeding and infant mental and motor development at one year. N Engl J Med 1989; 321:425-430

32. Rosen TS, Johnson HC: Children of methadone maintained mothers: Follow-up to 18 months of age. J Pediatr 1982; 101:192-196

33. Hayford SM, Epps RP, Dahl-Regis M: Behavior and development patterns in children born to heroin addicted and methadone maintained mothers. J Natl Med Assoc 1988; 80:1197-1200

34. Van Baar AL, Fleury P, Ultee CA: Behavior in first year of life after drug dependent pregnancy. Arch Dis Childhood 1984; 64:241-245

35. Bernstein VJ, Jeremy RJ, Hans SL, et al: A longitudinal study of offspring born to methadone maintained women—II: Dyadic interaction and infant behavior at four months. Am J Drug Alcohol Abuse 1984; 10:161-193

36. Jeremy RJ, Bernstein VJ: Dyads at risk: Methadone maintained women and their four month old infants. Child Devel 1984; 55:1141-1154

37. Wilson G: Clincal studies of infants and children exposed prenatally to heroin. Ann NY Acad Sci 1989; 562:183-194

38. Wilson G, McCreary R, Kean J, et al: The development of preschool children of heroin addicted mothers: A controlled study. J Pediatr 1979; 63:192-196

39. O'Keefe P: Preschool Program for Drug Exposed Infants—Perinatal Addiction Research and Education Update. Chicago, National Association for Perinatal Addiction Research and Education, 1989

40. Novello AC, Wise PH, Willoughby A, et al: Final report of the United States Department of Health and Human Services Secretary's Work Group on Pediatric Human Immunodeficiency Virus Infection and Disease: Content and implications. Pediatrics 1989; 84:547-555

41. Ochs HD: The human immunodeficiency virus-infected infant: A diagnostic dilemma (Editorial). Am J Dis Child 1989; 143:1138-1139

42. Centers for Disease Control: First 100,000 cases of acquired immunodeficiency syndrome—United States. JAMA 1989; 262:1453, 1456

43. Blanche S, Rouzioux C, Moscato ML, et al: A prospective study of infants born to women seropositive for human immunodeficiency virus type 1. N Engl J Med 1989; 320:1643-1648

44. Johnson JP, Nair P, Hines SE, et al: Natural history and serologic diagnosis of infants born to human immunodeficiency virus-infected women. Am J Dis Child 1989; 143:1147-1153

45. Des Jarlais DC, Friedman SR, Novick DM, et al: HIV-1 infection among intravenous drug users in Manhattan, New York City, from 1977 through 1987. JAMA 1989; 261:1008-1012

46. Selwyn PA, Schoenbaum EE, Davenny K, et al: Prospective study of human immunodeficiency virus infection and pregnancy outcomes in intravenous drug users. JAMA 1989; 261:1289-1294

47. Landesman SH, Minkoff HL, Willoughby A: HIV disease in reproductive age women: A problem of the present (Editorial). JAMA 1989; 261:1326-1327

48. Mondanaro J: Strategies for AIDS prevention: Motivating health behavior in drug dependent women. J Psychoactive Drugs 1987; 19:143-149

49. Bell NK: AIDS and women: Remaining ethical issues. AIDS Educ Prev 1989; 1:22-30

50. Siegel L, Korcok M: AIDS: The Drug and Alcohol Connection. Center City, Minn, Hazelden Foundation, 1989

**Addiction Medicine**
**and the Primary Care Physician**

# Drugs of Abuse—Opiates

WALTER LING, MD, *Los Angeles, and* DONALD R. WESSON, MD, *San Francisco*

*Treating opiate-dependent patients can be difficult for many physicians because the patients' lifestyles, values, and beliefs differ from those of the physicians. Primary care physicians, however, are often involved in the treatment of the medical complications of opiate abuse, and physicians must often manage a patient's opiate dependence until appropriate referral to a drug abuse treatment program can be arranged. Treatment is guided by an understanding of the patient's addictive disease, for which there are specific diagnostic criteria, and an understanding of the pharmacology of opiates of abuse and the medications used in treating opiate dependence. The opiate agonist, methadone, is useful for both detoxification and maintenance. The opiate antagonist, naloxone, is the treatment of choice for opiate overdose, and naltrexone, also an opiate antagonist, is a useful adjunct in subgroups of opiate-dependent patients for preventing relapse. New medications for the treatment of opiate dependence are being developed.*

(Ling W, Wesson DR: Drugs of abuse—Opiates, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:565-572)

The term opiate originally was used to refer to drugs that were derived from opium. Now it is often used interchangeably with the term "opioid," a more general term that includes both the natural and synthetic drugs of this type, including the antagonists.

The term "narcotics," which implies a state of stupor, originally referred to drugs that produced morphinelike analgesia. The term causes much confusion because it is sometimes used by law enforcement agencies to refer to any potent, abusable drug. Although the term "narcotic" may seem obsolete because of its lack of precision, its use is likely to continue.

Both morphine and codeine are contained in opium. Other opioids, such as heroin, oxymorphone, or hydromorphone, are semisynthetics derived from ingredients of opium. Some other opioids, such as meperidine, methadone, levomethadyl acetate (levo-$\alpha$-acetylmethadol), and fentanyl, are purely synthetics. There are also opiates known popularly as designer drugs, which are analogues of meperidine and fentanyl. (Several deaths resulted in the early 1980s from overdoses of $\alpha$-methyl fentanyl, and, more recently, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP], a neurotoxin from the synthesis of meperidine, caused acute parkinsonism in several abusers by destroying the dopamine-containing cells of the substantia nigra.) The term "designer drug," however, is not specific to opioids and may also refer to some nonopiates (such as methylenedioxymethamphetamine [MDMA]) manufactured in clandestine laboratories.

## Clinical Pharmacology

Opioids exert their effects by binding with one or more of several specific types of opioid receptors. The extent and predominance of this binding between the substance and the specific receptors determines the pharmacologic profile. The degree to which the resultant manifestations resemble the physiologic and psychological effects of morphine can be used to classify these substances. Those resembling morphine effects are called opioid agonists and those producing no opioid effects are called antagonists. Those in between are mixed agonist-antagonists or partial agonists. Most opioids in clinical use for pain management are opioid agonists, and all are subject to abuse. Several mixed agonist-antagonists and partial agonists also are widely used for pain relief, but, unfortunately, they are also subject to abuse. There are currently two antagonists available for clinical use. Naloxone hydrochloride (Narcan) is used primarily to reverse the effects of opioids, and naltrexone is used to treat some subgroups of opioid addicts.

Opioid receptors were first discovered in the 1970s, and their discovery has greatly facilitated the understanding of opioid pharmacology. Today opioid receptors are understood as a general class with a number of subtypes, but the major clinical pharmacologic effects of opioids are related primarily to several major receptor types—mu ($\mu$), kappa ($\kappa$), delta ($\delta$), and sigma ($\sigma$). $\mu$-Receptors have high binding affinity for morphinelike agonists. They mediate supraspinal analgesia, euphoria, physical dependence, respiratory depression, hypothermia, bradycardia, and miosis. Their activation suppresses the symptoms of opioid withdrawal. $\kappa$-Receptors, activated by butorphanol, nalbuphine, and pentazocine, mediate spinal analgesia, miosis, and sedation. Their activation does not invariably produce euphoria, but cessation after long-term administration does produce a withdrawal response as seen with $\mu$-agonists. $\delta$-Receptors also appear to mediate analgesia and appear to be the preferred site for endogenous opioid peptides. $\sigma$-Receptors may mediate the

From the Department of Psychiatry, University of California, Los Angeles, School of Medicine, and Los Angeles Drug Abuse Treatment Research Center (Dr Ling), and the Department of Psychiatry, University of California, San Francisco, School of Medicine, and Veterans Administration Medical Center, San Francisco (Dr Wesson).

This work was supported in part by National Institute on Drug Abuse (NIDA) grant DA 6082 to the Los Angeles Drug Abuse Treatment Research Center, administered by Friends Medical Science Research Center, Baltimore, and by NIDA grant DA 03516 to Merritt Peralta Institute, Oakland, California.

Reprint requests to Walter Ling, MD, 8447 Wilshire Blvd, Ste 409, Beverly Hills, CA 90211.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
FDA = Food and Drug Administration
HIV = human immunodeficiency virus
NIDA = National Institute on Drug Abuse

dysphoria produced by opioids and hallucinations, but its activation by the nonopioid phencyclidine raises questions of its being suitably classified as an opioid receptor.

Opioid receptors are widely distributed throughout the central nervous system. Those involved in pain and analgesia are in the locus ceruleus, the rapheal nuclei of the brain stem, the midbrain periaqueductal gray, and several hypothalamic and thalamic nuclei. Opioid receptors also appear in abundance in the dorsal horns of the spinal cord.

## Central Nervous System Effects of Opioids

Although opioids have substantial effects on a number of body organ systems, those of interest in terms of their abuse relate principally to their effects on the central nervous system. These include analgesia, euphoria, sedation, and respiratory depression. With repeated use, tolerance and physical dependence develop.

Opioid-produced analgesia is unique in that both perception and reaction to pain are altered. Not only is the pain threshold raised, but the subjects become indifferent to the pain. This unique indifference to pain appears to involve higher cortical centers, most likely the frontal cortical areas, because the effects resemble those seen after prefrontal lobotomy.

Euphoria, an exaggerated state of well-being and freedom from anxiety and distress, is invariably described by long-term users of opioids. The euphoric effect is not always experienced with initial opiate use. Indeed, many addicts recall their first experience as being unpleasant, often accompanied by nausea and vomiting. With repeated use, however, the pleasurable, floating sensation predominates, and the addict begins to seek the experience. Drowsiness and some clouding of mentation often accompany opioid use, and sleep may be induced, although more often there is simply a feeling of tranquility and sleepiness without actual sleep.

Respiratory depression results from inhibition of the brain-stem respiratory center by opioids. The major respiratory effect results from a reduced responsiveness to carbon dioxide accumulation. The respiratory pattern becomes slow and shallow. This respiratory effect can be partially overcome by external stimuli, and street addicts frequently use painful stimuli to help their friends overcome the respiratory depressive effects in cases of overdose.

TABLE 1.—*Characteristics of Opiate Agonists*

| *Medication, Generic Name (Trade Name[s])* | *Usual Single Dose for Pain, mg** | *Duration of Analgesia, h* | *How Abused* | *Abuse Liability* |
|---|---|---|---|---|
| Codeine | 30-60 | 3-4 oral | Oral<br>Injected | Low |
| Drocode (Synalgos-DC) | 16-32 | 3-4 | Oral | Moderate |
| Fentanyl citrate† (Sublimaze, Innovar‡) | 0.05-0.1 IM | 1-1.5 | Injected | High |
| Fentanyl analogues, anesthetic use | ... | ... | Injected | High |
| Alfentanil HCl (Alfenta) | | | | |
| Sufentanil citrate (Sufenta) | | | | |
| Diacetylmorphine (heroin) HCl | ...§ | | Snorted<br>Injected | High |
| Heroin freebase | | | Smoked | |
| Hydrocodone bitartrate (Anexsia, Azdone, Damason-P, Hycodan, Vicodin) | 5-10 oral | 3-4 | Oral | Moderate |
| Hydromorphone HCl (Dilaudid) | 2-4 oral<br>1-2 IM | 3-4 | Oral, tablets dissolved and injected | High |
| Levomethadyl acetate [formerly L-α-acetylmethadol] | ... | ... | Oral | Moderate |
| Levorphanol tartrate (Levo-Dromoran) | 2-3 oral<br>2-3 SC | 4-8 | ... | High |
| Meperidine HCl (Demerol,¶ Mepergan#) | 50-150 IM, or SC<br>100-200 oral | 3-4 | Injected | High |
| Methadone HCl | 2.5-10 oral | 3-5 | Oral | High |
| (Dolophine**) | 2.5-10 IM | 3-5 | | |
| Morphine sulfate | 10-15 IM | 3-4 | Injected | High |
| Opium | ... | ... | Smoked | Moderate |
| Oxycodone HCl (Percodan, Percocet) | 5-10 oral | 3-5 | Oral<br>Injected | Moderate |
| Oxymorphone HCl (Numorphan, injectable) | 1-1.5 IM | 4-6 | Injected | High |
| Propoxyphene HCl (Darvon, Dolene, Wygesic) | 32-64 oral | 3-4 | Oral | Moderate |
| Propoxyphene napsylate (Darvon-N) | 50-100 oral | 3-4 | Oral | Moderate |

HCl=hydrochloride, IM=intramuscularly, SC=subcutaneously

*Doses are for a nonopiate tolerant patient.
†Abused primarily by anesthesiologists. Fentanyl is sometimes available as a street drug of illicit manufacture known as "china white."
‡Fentanyl citrate in combination with droperidol, a sedating neuroleptic agent.
§Heroin has about 3 times the milligram potency of morphine
‖Investigational medication for the treatment of opiate dependency.
¶Meperidine hydrochloride is available as a pharmaceutically manufactured tablet, but the tablet is not a common street drug of abuse. Injectable meperidine is, however, a common drug of abuse by nurses and other health professionals.
#Meperidine hydrochloride in combination with promethazine hydrochloride.
**Dolophine is the injectable form. It is not a common street drug of abuse.

TABLE 2.—*Characteristics of Mixed Opiate Agonist-Antagonists*

| *Medication, Generic Name (Trade Name[s])* | *Usual Single Dose for Pain, mg* | *Duration of Analgesia, h* | *How Abused* | *Abuse Liability* |
|---|---|---|---|---|
| Buprenorphine hydrochloride* (Buprenex) | 0.3-0.6 IM | 6-8 | Injected | Moderate |
| Butorphanol tartrate (Stadol) | 1-4 IM | 3-4 | Injected | Moderate |
| | 0.5-2 SC | | | |
| Nalbuphine hydrochloride (Nubain) | 10 IM | 3-6 | Injected | Moderate |
| Pentazocine (Talwin Compound†) | 20-30 IM | 2-4 | Oral | Low |
| (Talwin, injectable) | 50 oral | 3-5 | Injected | Moderate |
| (Talwin Nx‡) | | | Injected | Low |

IM=intramuscularly, SC=subcutaneously

*Buprenorphine hydrochloride is being studied as an opiate maintenance medication. Its use for this purpose is investigational.
†A combination of pentazocine hydrochloride and aspirin.
‡A combination of pentazocine and naloxone hydrochloride. The naloxone will prevent the opiate agonist effect if the capsule is dissolved and injected. Taken orally, the naloxone has no effect.

Suppression of the cough reflex and constricted pupils are also well-known effects of opioids. Many opioids are excellent cough suppressants, and miosis, to which little tolerance develops, is useful in diagnosing opioid intoxication even in long-term users.

In general, opioid effects are qualitatively similar as a group. They differ, however, with respect to potency, duration of action, and relative effectiveness after oral administration. Mixed agonist-antagonists are qualitatively distinct from agonists. Tables 1 and 2 depict, respectively, the characteristics of the better known agonists and agonist-antagonists.

## Tolerance and Physical Dependence

At the cellular level, tolerance probably begins with the first dose of opioids, but it does not become clinically manifest until after repeated dosing of two to three weeks. Tolerance is best understood as the need for an increasing amount of the drug to achieve the same effect due to the progressive loss of effectiveness. The degree of tolerance depends on the interval between doses and the size of the dose: the larger the dose and the shorter the interval, the more pronounced the degree of tolerance. Tolerance, however, does not develop uniformly to all the pharmacologic effects of opioids. Notable tolerance develops quickly to analgesia, euphoria, sedation, and respiratory depression and only slightly and slowly to constipation and certain endocrine effects. It virtually does not develop to miosis. Nevertheless, tolerance is not complete to the euphoriant effect and to respiratory depression. For this reason, addicts continue to experience the desired sensation after each injection, and the danger of acute respiratory failure from overdose is ever present even in experienced addicts.

Cross-tolerance—the state in which a person tolerant to one opioid, such as morphine, is also tolerant to another similar opioid, such as methadone—develops with respect to the analgesic, euphoriant, sedative, and respiratory effects among opioids acting at the same receptor. Cross-tolerance does not appear to develop between opioids acting on different receptors. Tolerance to agonist-antagonist agents does not generally produce cross-tolerance with agonists, and tolerance does not develop to the antagonist effect of the mixed agonist-antagonist, nor to pure antagonists.

Physical dependence occurs concomitantly with the development of tolerance and is characterized by the appearance of a specific abstinence syndrome, with manifestations opposite to the acute effects of the drug. The mechanism of tolerance and physical dependence appears to be related to cellular adaptation, involving changes in the calcium flux or adenylate cyclase inhibition.

## Clinical Approach to Patient Assessment

A certain nonjudgmental attitude is necessary to effectively evaluate an addicted patient clinically. This is not always easy for physicians whose training tends to expose them to the devastating medical complications of drug abuse and addiction. Moreover, addicts conjure up images of thieves and criminals, and it is not always easy to separate the role of medicine from that of the justice system.

Most addicted persons can understand and accept the consequences of their own behavior, but, like children, they are irrationally sensitive to punishment and rejection. They may accept incarceration while resenting any suggestion that they have done something wrong to deserve the punishment. Understanding an addict's distorted perception of reality as part of his or her illness helps prevent the physician from becoming frustrated and prevents the addict from perceiving or misperceiving rejection on the part of the physician.

Because of addicted persons' general difficulty with authorities, they come to physicians with a certain degree of mistrust and resent having to seek help in this context. It helps to minimize the authoritarian structure in the initial encounter. It is important to avoid any interruption or distraction during the interview. Physicians become vulnerable under the pressure of time and subject to addicted patients' manipulations. Simple language is preferred. It is better to avoid using street terms unless the physician is certain of the terms' meanings. Hearing street terms misused makes addicts feel "one up" and tends to encourage their manipulative behavior.

An addicted patient should be assured of the confidential nature of the conversation, but questioning should be direct and to the point. Addicts will give reliable enough histories, although some allowances must be made. For instance, they will admit to having been in jail while explaining that they went to jail to protect a friend or that the judge made an error. They will rationalize but usually will not deny facts when questioned directly. They are not likely to volunteer any such information, however, and a systematic approach to history taking is necessary.

The drug abuse history should include information about the age of first use; periods of heavy use, periods of abstinence, and the surrounding life circumstances; the pattern of current use, including frequency, amount, and time of last

TABLE 3.—*Medical Syndromes in Opiate Abusers**

| *Syndrome (Onset and Duration)* | *Characteristics* |
|---|---|
| Opiate intoxication | Conscious, sedated, "nodding"; mood normal to euphoric; pinpoint pupils; history of recent opiate use |
| Acute overdose | Unconscious; pinpoint pupils; slow, shallow respirations |
| Opiate withdrawal | |
| Anticipatory† (3-4 hours after last "fix") | Fear of withdrawal; anxiety; drug craving; drug-seeking behavior |
| Early (8-10 hours after last "fix") | Anxiety; restlessness; yawning; nausea; sweating; nasal stuffiness, rhinorrhea; lacrimation; dilated pupils; stomach cramps; drug-seeking behavior |
| Fully developed (1-3 days after last "fix") | Severe anxiety; tremor; restlessness; piloerection‡; vomiting, diarrhea; muscle spasm§; muscle pain; increased BP; tachycardia; fever, chills; impulse-driven drug-seeking behavior |
| Protracted abstinence (may last up to 6 months) | Hypotension; bradycardia; insomnia; loss of energy, appetite; stimulus-driven opiate cravings |

BP=blood pressure

*The times given in the table refer to heroin. Withdrawal will develop slower with long-acting opiates such as methadone.
†Anticipatory symptoms begin as the acute effects of heroin begin to subside.
‡The piloerection has given rise to the term "cold turkey."
§The sudden muscle spasms in the legs have given rise to the term "kicking the habit."

use; previous treatments, voluntary or involuntary; any complications relating to health, job, family, or conflict with the law; and the concomitant use of other drugs and the pattern of their use. It is useful to ascertain what brings the patient into contact with the physician at this particular time. This information provides some useful insight into true motivation and helps the physician to formulate realistic treatment goals.

Addicts tend to exaggerate their drug use but to minimize their other life problems. The history, therefore, should be supplemented by careful observation and physical examination. Common physical findings include fresh needle marks and old scars; thrombosed veins; abscesses; swollen nasal mucosa; enlarged liver and lymph nodes; and signs of intoxication or withdrawal, depending on the time of the last "fix."

Virtually all opiate addicts have abnormal liver function. This should improve with treatment unless other complications, such as alcohol abuse, supervene. All patients should be encouraged to obtain testing for the human immunodeficiency virus (HIV) and appropriate counseling regarding the acquired immunodeficiency syndrome (AIDS). Other sexually transmitted diseases, also common among addicts, need attention as well.

A urine drug panel is useful to detect opioids, metabolites, and other drugs of abuse. The presence of morphine indicates recent use but is not diagnostic of physical dependence, which requires the presence of a specific abstinence syndrome.

Abstinence can be precipitated with the narcotic antagonist naloxone, but this has only limited clinical usefulness because its results are influenced by many, largely uncontrolled, variables. Among them are the regular doses of opioids, duration, size, the frequency of use, the timing and size of the last dose of opioid, the dose of naloxone, and the expectation of the patient. Without adequate control of these variables, the degree of physical dependence cannot be accurately determined, especially when it is most needed, as in cases of mild dependence. Most clinicians no longer rely on naloxone challenge as a diagnostic tool. A negative naloxone challenge test, however, remains a useful prerequisite to naltrexone induction.

## Clinical Diagnoses

A useful diagnostic distinction can be made between the maladaptive behavior associated with the regular use of opiates and the direct effects of the opiates on the central nervous system. The former consists of opioid dependence and opioid abuse. The latter includes the medical syndromes of opioid intoxication and opioid withdrawal. Acute overdose, a medical emergency, is a complication of acute intoxication. Table 3 summarizes some of the more common clinical features of opioid intoxication, acute overdose, and opioid withdrawal.

The American Psychiatric Association's diagnostic criteria now consider the central features of opioid dependence as a cluster of cognitive, behavioral, and physiologic symptoms that indicate impaired control over drug use and continued use despite adverse consequences.[1]

The presence of tolerance and withdrawal alone does not suffice for the diagnosis. Nine characteristic symptoms, with a time element, constitute the diagnostic criteria. A minimum of three symptoms must be present for a definite diagnosis. A set of criteria for rating the severity of the disorder is also provided.

### *Diagnostic Criteria for Opioid Dependence*

At least three of the following must be present:

- Opioids are taken in larger amounts or over a longer period than the person intended;
- A desire for the drug persists, or the patient has made one or more unsuccessful efforts to cut down or to control opioid use;
- A great deal of time is spent in activities necessary to obtain opioids (such as theft), taking the drug, or recovering from its effects;
- The patient is frequently intoxicated or has withdrawal symptoms when expected to fulfill major role obligations at work, school, or home (for example, does not go to work, goes to school or work "high," is intoxicated while taking care of his or her children) or when opioid use is physically hazardous (such as driving under the influence);
- Important social, occupational, or recreational activities are given up or reduced;
- Continues opioid use despite the knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by the use of opioids (for instance, keeps using heroin despite family arguments about it);
- Marked tolerance: needs greatly increased amounts of the drug—at least a 50% increase—to achieve the desired effect, or a notably diminished effect occurs with continued use of the same amount;

• Has characteristic withdrawal symptoms (see opioid withdrawal syndromes in Table 3);

• Opioids are often taken to relieve or avoid withdrawal symptoms.

In addition, some symptoms of the disturbance have persisted for at least a month or have occurred repeatedly over a longer period to time.

*Criteria for Severity of Opioid Dependence*

The following criteria are used to determine the severity of opioid dependence:

*Mild.* Few, if any, symptoms are present in excess of those required to make the diagnosis, and the symptoms result in no more than mild impairment in occupational functioning or in usual social activities or relationships with others.

*Moderate.* Functional impairment or symptoms are between "mild" and "severe."

*Severe.* Many symptoms are present in excess of those required to make the diagnosis, and the symptoms greatly interfere with occupational functioning or usual social activities or relationships with others.

*In partial remission.* During the past six months, there has been some use of the substance and some symptoms of dependence.

*In full remission.* During the past six months, either there has been no use of opioids, or opioids have been used and there were no symptoms of dependence.

*Opioid Abuse*

Opioid abuse is now considered a residual category of the maladaptive pattern of opioid use that does not meet the diagnostic criteria of opioid dependence. The central feature is a continued use of the drug despite persistent and recurrent social, occupational, psychological, or physical problems caused by the use of the drug. A time element is also included.

*Diagnostic Criteria for Opioid Abuse*

A maladaptive pattern of opioid use is indicated by at least one of the following:

• There is continued use despite a knowledge of having a persistent or recurrent social, occupational, psychological, or physical problem that is caused or exacerbated by the use of opioids;

• There is recurrent use in situations in which opioid use is physically hazardous (such as driving while under the influence of opioids).

Other criteria are that some symptoms of the disturbance have persisted for at least a month or have occurred repeatedly over a longer period of time, or the patient clearly takes opiates but never met the criteria for opioid dependence.

## Treatment of Opioid-Induced Medical Syndromes

*Opioid Intoxication*

Unless medical complications supervene, addicts do not seek treatment for their intoxicated state. The syndrome is not uncommonly seen at drug treatment clinics, however, and clinical observation is prudent, although no specific intervention is required. The presence of intoxicated addicts in the clinic vicinity should alert a physician to the possibility of drug diversion.

*Acute Overdose*

Coma, pinpoint pupils, and slow—four to five per minute—shallow respirations are the classic triad of acute opioid overdose. The response to the intravenous administration of naloxone hydrochloride (0.4 to 0.8 mg) is diagnostic. A comatose patient regains full consciousness within seconds of the naloxone injection and frequently shows some signs of opiate withdrawal. This clinical characteristic is so specific that anything less dramatic suggests mixed-drug overdose or other causes of coma. Signs of precipitated opiate withdrawal, when present, usually pass quickly without a specific intervention. Slow injection will avoid the confusion and agitation that sometimes accompany too rapid a return to consciousness.

Naloxone is the treatment of choice for opioid overdose. It should be given intravenously and, after the initial dose, titrated according to the patient's clinical response. Naloxone is short-acting; its effects last from 15 to 20 minutes. The opioids causing coma, such as methadone, may be much longer-acting, and the patient may lapse back into coma as the antagonist effect diminishes. Patients should not be discharged after the initial response but should be observed at least several hours. If long-acting opioids such as methadone or levomethadyl acetate are involved, the patient should be admitted to a hospital.

*Opioid Withdrawal and Detoxification*

The severity of withdrawal symptoms is determined by the degree of physical dependence and environmental influences. Experiences from therapeutic communities suggest that most opiate addicts can undergo withdrawal in a supportive, structured environment without medications. The symptoms of withdrawal are likened to a bout of influenza under these circumstances.

Drug cravings can be intense during withdrawal and often will lead to relapse if drugs are available. Contrary to the belief of many addicts and some physicians, the craving occurs not because of the absence of drugs but, rather, because of their potential availability. When drugs are truly unavailable, cravings usually subside quickly.

At present, the two most commonly used medications for detoxification are methadone and clonidine. Methadone is widely used for outpatient detoxification in methadone treatment clinics. The underlying principle is simple and straightforward. A longer-acting opioid, methadone, given orally once daily, generally in doses as high as 30 mg, is substituted for the opioids of abuse: heroin, meperidine, codeine, and the like. The patient is stabilized for several days, and the methadone is then gradually withdrawn. Although federal regulation now allows methadone detoxification to extend as long as 180 days,[2] California and most other states restrict methadone detoxification to 21 days. With a 21-day methadone detoxification of persons with a long-term opioid addiction, only a few patients achieve opiate abstinence, and, for those who do, relapse is frequent.

Many opiate addicts use outpatient methadone detoxification to lower the level of their physical dependence. Clinicians view the treatment as a humane exercise and an opportunity to bring the addict into contact with the drug abuse treatment system, in the hope that the addict will eventually commit to long-term treatment.

Methadone is a schedule II narcotic subject to stringent Food and Drug Administration (FDA) control. Under the

law, physicians are not permitted to prescribe it for the treatment of opioid addiction except in the context of a specially licensed program or unless the patient has an acute, concurrent medical condition.

Clonidine, an $\alpha$-adrenergic agonist that suppresses opiate withdrawal, is not a scheduled medication. Although not FDA-approved for treating opiate withdrawal, clonidine is now commonly prescribed by private physicians and drug treatment programs for opiate detoxification. It is not an opiate, does not produce euphoria, and is not subject to abuse. When used for short-term opiate detoxification, clonidine does not produce physical dependence and can be discontinued with ease.[3,4]

One recommended regimen is to begin with 0.2 mg of clonidine hydrochloride given orally every four to six hours on the first day. The dose is adjusted to between 0.8 and 1.2 mg per day in divided doses for the next seven to ten days and tapered off over two to three days. Drowsiness and dizziness, from postural hypotension, are common side effects. Patients should be warned not to drive or operate machinery should drowsiness occur. Dizziness from postural hypotension can be relieved by lying down. The blood pressure should be monitored, and clonidine is withheld if the blood pressure falls to 90/60 mm of mercury or below.

Clonidine appears to be most effective in patients with signs of withdrawal. It is helpful for patients to learn this firsthand by an appropriate timing of the initial dose. A transdermal clonidine patch is now available and can be used in combination with oral clonidine in the following manner: Patients showing objective signs of withdrawal are given 0.2 mg of oral clonidine sublingually and two or three #2 clonidine transdermal patches—two if the patient weighs less than 68 kg (150 lb), three if more than 68 kg. The sublingual dose is repeated in an hour if the signs of withdrawal persist. Otherwise patients receive 0.2 mg of clonidine orally every six hours for the next two days. The patches are left for seven days for heroin withdrawal and ten days for methadone withdrawal.[5,6]

Suppression of the withdrawal syndrome by clonidine is incomplete. Ancillary medications for pain (acetaminophen or ibuprofen) and sleep (chloral hydrate), used judiciously, are generally effective.

Recidivism is high among addicts with established physical dependence whether detoxification is accomplished with methadone, clonidine, or some other method. In view of the current AIDS epidemic and the high risk of HIV exposure from continued "street" drug use, it would appear that detoxification alone does not suffice but should be used as a transitional step towards a longer-term treatment plan, which may include treatment with methadone, levomethadyl, buprenorphine, or naltrexone.

## Treatment of Opioid Dependence

### *Methadone Maintenance*

Methadone, in use since the 1960s, is covered elsewhere in this issue of the journal.* It is the only opioid presently approved by the FDA for the long-term treatment of opioid dependence.

### *Levomethadyl Acetate*

Levomethadyl acetate (formerly levo-$\alpha$-acetylmethadol), first synthesized in the 1940s, is a congener of methadone. It has been extensively studied, and there is an ongoing effort by the National Institute on Drug Abuse (NIDA) to make it available for general clinical use. It is an effective analgesic with some unique characteristics: it has a delayed onset and a long duration of action, and, because of its biotransformation in the liver, it is relatively more effective after oral, rather than parenteral, administration.

Clinical interest in levomethadyl as an alternative to methadone prompted a series of clinical trials by individual investigators and three large-scale multiclinic studies. The results of these investigations suggest that levomethadyl is comparable to methadone in clinical safety and efficacy but has a number of advantages. Pharmacologically, levomethadyl itself is relatively inactive, and its slow onset of action after parenteral administration makes it less subject to abuse by street addicts seeking an instant "high." Its long duration of action allows for three-times-per-week clinic attendance without take-home medications, thus eliminating the street diversion of take-home doses. Fewer clinic visits increase a clinic's treatment capacity and reduce patients' feelings of dependence on the clinic. Because take-home privileges no longer are an issue, patients are less compelled to lie to staff to protect their take-home privileges, and a more open, honest atmosphere prevails at the clinics. Because of its slower onset and more sustained action, patients feel less sedated.

No significant adverse effects were noted in the three large clinical trials with more than 3,500 patients, some treated for a year and longer. Other studies also support the drug's clinical safety.[7,8]

Only a few women have been treated with levomethadyl.[9] More experience in treating women with this drug is needed in view of the increasing number of opiate-dependent women seeking treatment.

Because levomethadyl is an orphan drug, the responsibility for filing a new drug application falls on the NIDA. A submission to the FDA was made in September 1979, but little has happened in the ensuing years. Recently the NIDA has initiated new efforts to complete the new drug application process, and it is hoped that levomethadyl will become available for general clinical use soon.

### *Naltrexone*

Naltrexone is related to naloxone (Narcan), the only other currently available pure narcotic antagonist. It is produced by substituting the *N*-allyl of naloxone with the cyclopropylmethyl radical of another antagonist, cyclazocine, thus combining the relatively pure antagonist action of the former and the long duration of action and oral effectiveness of the latter. Clinical trials in the 1970s and early 1980s indicate that naltrexone can be a useful adjunct in the treatment of opioid dependence.[10,11] It was approved by the FDA for general use in 1984 and is available under the trade name Trexan.

Naltrexone comes as close to being an ideal narcotic antagonist as can be hoped for. It is quickly absorbed after oral administration, reaching a peak plasma concentration within an hour, and begins to work even sooner. Its effects are long-lasting; a single oral dose of 50 mg blocks the euphorigenic effects of a 25-mg dose of heroin for as long as 24 hours, and 150 mg provides blockage for as long as 3 days. It does not produce euphoria or cause dysphoria. It is not addicting, has no street value, and addicts do not abuse it.

The clinical use of naltrexone, however, is not without problems. It cannot be administered to addicts for as long as

*J. E. Zweben, J. T. Payte, "Methadone Maintenance in the Treatment of Opioid Dependence—A Current Perspective," pp 588-599.

there is opioid in their systems. This means that for most addicts, naltrexone cannot be prescribed for them when they first seek treatment as most addicts come to treatment with a history of recent use. Detoxification using methadone, clonidine, or some other method is a prerequisite of naltrexone therapy for most addicts.

An opioid-free interval is necessary to avoid a precipitated withdrawal by the initial dose of naltrexone. An interval of 5 to 7 days is recommended for heroin and 10 to 14 days for methadone. The period can be shortened somewhat by giving repeated doses of naloxone. The technique is not altogether innocuous, and it is advisable for physicians to familiarize themselves with it first by working with an experienced physician.

The drug-free state should be verified by administering a naloxone challenge. One method is to place 0.8 mg of naloxone in a syringe and administer 0.2 mg of it intravenously followed by a 30-second observation period for any symptoms or signs of withdrawal. If none are observed, the remaining 0.6 mg is given and the patient observed for an additional 20 minutes, during which symptoms and signs of withdrawal and vital signs are serially recorded. A worksheet can be constructed for this purpose to allow some quantification of the results. If a patient shows even minor symptoms and signs of withdrawal, he or she will likely not tolerate the initial dose of naltrexone, and the procedure should be repeated 24 hours later. If a negative test results, the patient can be administered an initial dose of 25 mg (half a tablet) of naltrexone and observed for another hour. If all goes well, the other 25 mg (half a tablet) can be given, bringing the first daily dose to 50 mg. Thereafter, several dosage schedules are available: Naltrexone can be given 50 mg daily; 100 mg Monday and Wednesday, and 150 mg Friday; or 150 mg Monday and 200 mg Thursday.

Naltrexone is well tolerated and side effects are uncommon. The manufacturer of the medication, DuPont Pharmaceuticals, has prepared a product monograph summarizing the results of most major clinical trials. There are also educational materials for physicians and patients. These are useful and may be obtained from representatives of the manufacturer.

Once a naltrexone regimen is initiated, patients cease craving and using opiates. This relates to the complete blockage of the euphorigenic effect of opiates by naltrexone. It is as though the patients realize that drugs (drug effect in this case) are truly no longer available. It is good clinical strategy to teach patients the relationship between the availability of drugs and craving. When an addict's access to an opiate effect is made unavailable by naltrexone, opiate craving ceases.

While naltrexone's ability to block the effects of opiates is certain, its place in the long-term treatment of opioid addicts is limited by low patient acceptance and by the high failure rates of opiate detoxification—a necessary first step to naltrexone treatment. Certain subgroups of patients, physicians, and other professionals, for instance, and other people with a higher socioeconomic status do better with naltrexone than do "street" addicts.[12] The reasons are not always clear but probably relate to their having a great deal more to lose, so to speak, and having experienced successful drug-free lives before. Many physicians are able to practice while receiving naltrexone, and, for some, the drug has been lifesaving.

Many addicts, while well motivated, are unable to resist the urge to use drugs after detoxification long enough to allow naltrexone induction. Buprenorphine may offer new hope.

*Buprenorphine Hydrochloride*

Buprenorphine hydrochloride, a partial agonist analgesic with both agonist and antagonist effects, has been undergoing clinical investigation for the treatment of opioid dependence for more than a decade. A parenteral form of the drug (Buprenex) has been approved by the FDA for the relief of moderate to severe pain, but its use for the treatment of opioid dependence remains investigational.

Buprenorphine blocked the effects of morphine in early clinical trials with addicts. Naloxone administration did not precipitate acute withdrawal in patients treated with buprenorphine. Abrupt discontinuation after eight weeks of buprenorphine treatment resulted in only a mild morphine-like withdrawal, and, while taking buprenorphine, subjects stopped the self-administration of heroin.[13,14]

In another study, 2 mg of buprenorphine was given subcutaneously to eight subjects in place of their daily dose of methadone (mean daily dose of 36 mg). Only mild discomfort resulted, and after 28 days of buprenorphine administration, an abrupt placebo substitution resulted in a mild withdrawal syndrome of several days' duration.[15] In a double-blind short-term study, 2 mg of sublingual buprenorphine was found to be comparable to 30 mg of methadone.[16] Illicit opioid use in this study was common and suggests a need for a higher dosage.

More recently, in a 30-day outpatient open-label clinical trial, buprenorphine in doses of 2, 4, and 8 mg given sublingually was effective in maintaining abstinence and keeping patients in treatment. At the conclusion of the trial, the buprenorphine administration was abruptly discontinued. Patients maintained on the 8-mg dose had a substantial increase of withdrawal symptoms. Those on 2- and 4-mg doses had only minimal withdrawal, and 7 of the 16 patients were successfully started on a regimen of naltrexone.[17]

These clinical trials involved only a small number of patients, and they need to be confirmed with controlled studies of larger numbers. The results thus far, however, are promising and suggest that buprenorphine could be an effective agent for detoxification as well as maintenance. If further studies confirm that patients can be abruptly switched from buprenorphine to naltrexone, buprenorphine can become a useful transitional drug from street heroin and methadone to naltrexone.

There has been a great deal of excitement surrounding the recent observation that using buprenorphine may reduce cocaine use.[18,19] Because cocaine abuse is found in as many as 40% of methadone-treated opioid addicts, substituting buprenorphine may reduce cocaine abuse in this population. There is also some suggestion that antagonists may reduce alcohol consumption. It would be of interest to know if buprenorphine, a partial agonist, will also reduce drinking, a major problem among methadone-maintenance patients because an opiate antagonist cannot be used with these patients.

Buprenorphine is not entirely free of abuse liabilities, although it may be less addictive than methadone. Some buprenorphine abuse by addicts has been reported in Europe and Australia where the drug is available in a tablet form.[20,21]

### *Therapeutic Community*

Therapeutic communities for opioid addicts began in 1958 with the founding by Charles Diderich of the Synanon Foundation in Santa Monica, California. Today's therapeutic communities are highly structured residential treatment facilities. While treatment philosophy may differ from one therapeutic community to another, virtually all stress a complete abstinence from all drugs and strictly prohibit physical violence. Most therapeutic communities now embrace a 12-step recovery process similar to that of Alcoholics Anonymous, and most programs emphasize restructuring of lifestyles and resocialization through self-reliance, self-disclosure, peer pressure, and peer support. A detailed description of their philosophies, target population, and treatment approaches is beyond the scope of this article. A good general summary has been published by De Leon and Rosenthal.[22]

#### REFERENCES


1. Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed, Revised. Washington, DC, American Psychiatric Association, 1987

2. Methadone: Rules and regulations. Federal Register 1989; 54:8954-8971

3. Gold MS, Pottash AC, Sweeney DR, et al: Opiate withdrawal using clonidine—A safe, effective, and rapid nonopiate treatment. JAMA 1980; 243:343-346

4. Washton AM, Resnick RB, Rawson RA: Clonidine for outpatient detoxification (Letter). Lancet 1980; 1:1078-1079

5. Smith DE, Wesson DR, Tusel DJ: Detoxification, chap 4, *In* Treating Opiate Dependency. Center City, Minn. Hazelden Foundation, 1989, pp 45-59

6. Spencer L, Gregory M: Clonidine transdermal patches for use in outpatient opiate withdrawal. J Subst Abuse Treat 1989; 6:113-117

7. Ling W, Blaine JD: The use of LAAM in treatment, chap 7. *In* Dupont RL, Goldstein A, O'Donnell J (Eds): Handbook on Drug Abuse. Government Printing Office, 1979, pp 87-96

8. Blaine JD, Thomas DB, Barnett G, et al: Levo-α-acetylmethadol (LAAM): Clinical utility and pharmaceutical development, chap 28, *In* Lowinson JH, Ruiz P (Eds): Substance Abuse: Clinical Problems and Perspectives. Baltimore, Williams & Wilkins, 1981, pp 360-388

9. Hargreaves WA, Ling W, Brown TC, et al: Women on LAAM maintenance: Initial experiences. J Psychedelic Drugs 1979; 11:223-229

10. Martin WR, Jasinski DR, Mansley PA: Naltrexone, an antagonist for the treatment of heroin dependence. Arch Gen Psychiatry 1973; 28:784-791

11. Report of the National Research Council Committee on Clinical Evaluation of Narcotics Antagonists: Clinical evaluation of naltrexone treatment of opiate-dependent individuals. Arch Gen Psychiatry 1978; 35:335-340

12. Ling W, Wesson DR: Naltrexone treatment for addicted health-care professionals: A collaborative private practice experience. J Clin Psychiatry 1984; 45:46-48

13. Jasinski DR, Pevnick JS, Griffith JD: Human pharmacology and abuse potential of the analgesic buprenorphine. Arch Gen Psychiatry 1978; 35:501-516

14. Mello MK, Mendelson JH, Kuehnle JC: Buprenorphine effects on human heroin self-administration: An operant analysis. J Pharmacol Exp Ther 1982; 223:30-39

15. Jasinski DR, Henningfield JE, Hickey JE, et al: Progress report of the NIDA Addiction Research Center, Baltimore, Md, 1982—The Committee on Problems or Drug Dependence. Natl Inst Drug Abuse Res Monogr Ser 1983; 43:92-98

16. Bickel WK, Stitzer ML, Bigelow GE, et al: A clinical trial of buprenorphine: Comparison with methadone in the detoxification of heroin addicts. Clin Pharmacol Ther 1988; 43:72-78

17. Kosten TR, Kleber HD: Buprenorphine detoxification from opioid dependence: A pilot study. Life Sci 1988; 42:635-641

18. Kosten TR, Kleber HD, Morgan C: Role of opioid antagonists in treating intravenous cocaine abuse. Life Sci 1989; 44:887-892

19. Mello NK, Mendelson JH, Bree MP, et al: Buprenorphine suppresses cocaine self-administration by rhesus monkeys. Science 1989; 425:859-862

20. O'Connor JJ, Maloney R, Travers R, et al: Buprenorphine abuse among opiate addicts. Br J Addict 1988; 83:1085-1087

21. Quigley AJ, Bredemeyer DE, Seow SS: A case of buprenorphine abuse. Med J Aust 1984; 140:425-426

22. De Leon G, Rosenthal MS: Treatment in residential therapeutic communities, chap 138, *In* American Psychiatric Association Task Force: Treatment of Psychiatric Disorders. Washington, DC, American Psychiatric Assoc, 1989, pp 1379-1416

**Addiction Medicine**
**and the Primary Care Physician**

# Pharmacologic Approaches to the Treatment of Cocaine Dependence

WANDA A. TAYLOR, MD, *and* MARK S. GOLD, MD, *Summit, New Jersey*

*When pharmacologic agents are considered in the treatment of cocaine addiction, the objective of such treatment—sustained abstinence—must be considered. Medication and medical approaches have been disappointing in the treatment of cocaine overdose. The central neurobiologic mechanism(s) involved in cocaine toxicity are poorly understood. Without a cocaine antagonist, pharmacologic approaches have been less than promising in preventing relapse. Various psychoactive medications have been tried in early cocaine abstinence, with some success.*

(Taylor WA, Gold MS: Pharmacologic approaches to the treatment of cocaine dependence, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:573-577)

There has been a resurgence in the use of cocaine, and this has caused havoc in our neighborhoods, schools, family, legal system, and on our peace of mind. Reports of the use of this alkaloid go back many centuries.[1] The Incas in South America chewed coca leaves and referred to cocaine as a "gift from the Sun God." With the Spanish Inquisition, the rulers first prohibited the use of this drug but then later promoted it because of difficulties "motivating" Indian mine workers. In fact, these conquerors became the largest cultivators of cocaine in South America.[2]

It was the Austrian scientist Albert Nieman in 1860 who isolated the cocaine alkaloid, and the famous self-experiments of Freud provided much knowledge regarding the physiologic effects of cocaine. Freud, however, also used this amazing drug to "cure" many psychiatric ailments from depression, hysteria, and digestive disorders to ailments such as alcoholism and opiate addiction.[3]

The continued use of cocaine into the early 20th century brought "cure-all" formulas such as Vin Mariani, a wine made by Angelo Mariani that contained cocaine. This wine received endorsements from famous figures such as Pope Leo XVIII and Thomas Edison. The other widely known formula, Coca-Cola, contained cocaine as its active ingredient until the Pure Food and Drug Act of 1906.[4] The horrors of cocaine addiction were all too clear. With the Harrison Narcotic Act of 1914, cocaine was banned, and this drug has been underground since then. Cocaine use lost its popularity until its resurgence in the 1970s.[2,5]

What makes this drug so enticing and has led to a resurgence of use is multifactorial:

- Multiple perceived freedoms—the 1960s were a time of experimentation in instant pleasure-seeking with sex and drugs;
- Increased production in South America;
- Increased dose—presumably a purer cocaine is being seen as a result of this increased production. In the 1970s cocaine was often adulterated in street preparations, with the amount of cocaine ranging from 10% to 50%[6];
- Decreased price—promoting use in a younger-aged and lower socioeconomic population;
- Drug effect—cocaine is a powerful reinforcing agent because of its biochemical and psychological properties; and
- Innovations in drug delivery—freebase, or "crack"—deliver drugs in concentrations and a latency previously reported only for intravenous use.

In this article we will address the medical consequences of freebase cocaine use and the current pharmacologic adjuncts in treatment.

## Medical Complications

There are several routes of cocaine self-administration: intranasal, intravenous, oral, pulmonary, and applying to various mucous membranes—oral, genital, or rectal. The intensity, immediacy, and duration depend on the route and quantity used (Table 1).

Regardless of the route used, the initial central nervous system (CNS) effect is one of euphoria: the user is alert and full of self-confidence. This CNS effect is brief, and what remains with increasing intoxication is insomnia, anorexia, feelings of grandeur, malnutrition, aggressiveness, impaired judgment, and hypersexuality. Other symptoms include irritability, depression, fatigue, poor concentration, panic,[7-9] and a paranoid psychosis.

Several of the medical complications are related to the route of use,[10] as, for example, perforation of the nasal septum due to vasoconstriction in the nostrils causing inflammation and ulcerations. In those who smoke cocaine, there is evidence of obstructive airway disease.[11] Nathan and coworkers did spirometric measurements and measured the diffusing capacity of the lungs for carbon monoxide on 22 subjects with a heavy history of "freebasing." A third of these subjects had evidence of obstructive airway disease.[11]

Although cocaine overdose has been thought to be rare, it is becoming far more common. A study by the National Institute on Drug Abuse has shown a significant rise in drug-related emergency department visits through 1988, in which

From Fair Oaks Hospital, Summit, New Jersey.
Reprint requests to Wanda A. Taylor, MD, Fair Oaks Hospital, 19 Prospect St, Summit, NJ 07901.

TABLE 1.—*Differential Effects Dependent on Routes of Cocaine Administration*

| Administration: Route | Administration: Mode | Initial Onset of Action, s | Duration of "High," min | Average Acute Dose, mg | Peak Plasma Levels, ng/ml | Purity, % | Bioavailability, % absorbed |
|---|---|---|---|---|---|---|---|
| Oral | Coca leaf chewing | 300-600 | 45-90 | 20-50 | 150 | 0.5-1 | ... |
| Oral | Cocaine HCl | 600-1,800 | | 100-200 | 150-200 | 20-80 | 20-30 |
| Intranasal | "Snorting" cocaine HCl | 120-180 | 30-45 | 5×30 | 150 | 20-80 | 20-30 |
| Intravenous | Cocaine HCl | 30-45 | 10-20 | 25-50 | 300-400 | 7-100 | 100 |
| | | | | >200 | 1,000-1,500 | ×58 | |
| Smoking, intrapulmonary | Coca paste | 8-10 | 5-10 | 60-250 | 300-800 | 40-85 | 6-32 |
| | Freebase | | | 250-1,000 | 800-900 | 90-100 | |
| | Crack | | | | ? | 50-95 | |

HCl = hydrochloride

the number of substance abuser emergency department contacts because of drug overdose was 41.1%. This increase has occurred nationwide from 1987 to 1988, with the number of cocaine-related incidents up by 37.4% and 39.4% in the Northeast and West, respectively, and by 50.7% and 17% in the southern and central regions, respectively ("Drug Study Finds Regional Basis," *USA Today*, November 16, 1989).[12] These data, which were compiled from 26 metropolitan areas, also revealed a 38.5% rise in drug abuse deaths involving cocaine use.

Overdose can occur from any route and at any time and is not related to long-term use. One clue to this phenomenon is the finding of several studies of animals that show hyperthermia to be an important contribution to cocaine death.[13] This hyperthermia may occur through central thermoregulatory mechanisms as well as peripheral mechanisms such as vasoconstriction and increased muscle activity.[13] Life-threatening cardiac arrhythmias and seizure activity can result from hyperpyrexia. Gold and associates suggest vigorously cooling these patients. They found that the administration of bicarbonate may be contraindicated in the treatment of cocaine-related metabolic acidosis; the intravenous administration of sodium bicarbonate lowered the amount of cocaine required to produce a major seizure by 18%.[13]

The morbidity from cocaine overdose can be complicated by the concomitant involvement of other drugs such as amphetamines, barbiturates, opiates, and alcohol.[14,15] Cardiovascular complications include myocardial infarction, arrhythmias, and asystole. Central nervous system complications include stroke, subarachnoid hemorrhage, hyperpyrexia, seizures, and fungal cerebritis.[16,17] Ischemic bowel results from vasoconstriction of the mesenteric vasculature. Deaths have been reported from the accidental rupture of bags filled with cocaine by people who had swallowed them in attempting to smuggle the drug through customs.[15] Pneumopericardium and spontaneous pneumomediastinum have been reported. Administering cocaine through contaminated needles can lead to hepatitis, endocarditis, and the acquired immunodeficiency syndrome.[18,19] Rhabdomyolysis has been reported.[20] Sexual dysfunction may result from cocaine-induced hyperprolactinemia.[21,22]

Women of childbearing age have become an increasing proportion of cocaine abusers.[23] The New York State Division of Substance Abuse Services has revealed that 34% of crack addicts admitted to publicly financed programs are women.[24] In New York City from 1986 through 1988, the number of babies born with drugs in their urine has tripled. Chasnoff and co-workers studied 75 pregnant cocaine users and the perinatal outcome. Those women who used cocaine throughout their pregnancy had higher rates of preterm deliveries and infants with low birth weights.[25] There was also a higher rate of intrauterine growth retardation. These effects may be due to placental vasoconstriction decreasing the flow of blood to the fetus. There are also reports of neonatal seizures, cerebral infarctions, and birth defects.[25,26]

## Biochemistry

For cocaine to produce its euphoric and rewarding effects, the integrity of the dopaminergic tracts originating in the midbrain ventral tegmental area projecting to the mesolimbic and mesocortical pathways must be maintained.[27,28] This theory is supported by drug self-administration studies in animals where destruction of the nucleus accumbens blocks intracranial cocaine self-administration. The mesolimbic pathway, which includes the nucleus accumbens, and the mesocortical pathway, which includes the frontal cortex, are integral to the reward-mediating function in the brain. Cocaine activates the dopaminergic circuits in the brain.[29] These circuits can be blocked by agents such as neuroleptic drugs and neurotoxins such as 6-hydroxydopamine, which in turn diminishes or blocks the euphoric effects of cocaine.[28,30]

Dopamine is released by a complex mechanism at the neurons.[29] After its release, it is taken back up into the neuron and stored for further use. Cocaine blocks the reuptake of dopamine into the neuron. In the initial use of cocaine, this reuptake blockade leads to an increased exposure of dopamine on the neuron, with resultant euphoria. With long-term use, however, a different pattern is found. When dopamine is released into the synapse, a portion is recycled, but a certain portion of it is metabolized in the synapse by catechol-*o*-methyltransferase, which cannot be recycled to dopamine.[31] Chronic cocaine exposure depletes the dopamine in the brain by blocking its reuptake and thus increasing synaptic metabolism by catechol-*o*-methyltransferase, leaving less dopamine for recycling.[28,29]

The overall effect of regular use is to decrease the amount of the total available dopamine in the brain. There is evidence of postsynaptic hypersensitivity in response to this chronic depletion.[29] This depletion of dopamine and the hypersensitivity of postsynaptic neurons are felt to relate to the craving that occurs with long-term cocaine use.

Other neurochemical systems involved in the effects of cocaine include norepinephrine. Cocaine inhibits the reuptake of norepinephrine, which is analogous to the effect on the dopamine system. The major mechanism in clearing norepinephrine from the synapse is by reuptake and recycling the neurotransmitter. This norepinephrine reuptake blockade leads to an accumulation of norepinephrine in the synapse

and the resultant stimulatory effects on the norepinephrine system. This stimulatory effect may be responsible for the adrenergic effects seen with cocaine intoxication, such as tachycardia, hypertension, increased sweating, mydriasis, and tremors.

Just as with dopamine, the long-term administration of cocaine leads to norepinephrine depletion. This is felt to explain the occurrence in cocaine users of "crushing" depressive symptoms, suicidal tendencies, poor concentration, sleep and appetite disturbances, decreased sexuality, and anhedonia.[15]

Cocaine's effect on serotonin (5-hydroxytryptamine) is predominantly inhibitory. It blocks reuptake and reduces concentrations of serotonin and its metabolites. There is also a reduction in tryptophan hydroxylase activity and the availability of precursors. The net result is a reduction in the synthesis and turnover of serotonin in the brain.[15]

Although the major known effects of cocaine are on the dopamine, norepinephrine, and serotonin systems, there seems to be other biochemical involvement as well. It appears that the opioid peptides may play a role in the effects of cocaine. Naloxone, an opiate antagonist, can increase the stimulatory and euphoric effects of cocaine.[32] Other neuroactive substances under investigation are vasopressin, $\gamma$-aminobutyric acid, acetylcholine, the calcium-calmodulin system, and phenylethylamine, which is an endogenous amine.[33]

## Pharmacology

Cocaine use is a major public health problem in the United States. It has had far-reaching effects on our health, legal, family, and financial systems. Treatment has taken a comprehensive approach, taking into account these multifactorial problems to include education, relapse prevention measures, peer support groups, family therapy, 12-step programs, and urine monitoring to assess abstinence. New pharmacologic treatments have been developed as adjuncts to the treatment of cocaine addiction. The objectives of such treatment are to obtain and sustain abstinence. In addressing the biologic aspects of cocaine abuse, one pharmacologic approach has been toward lessening the cocaine withdrawal symptoms, dysphoria, and craving.

TABLE 2.—*Bromocriptine Mesylate Regimen for Cocaine Withdrawal**

| Day | Bromocriptine Dose, mg | Frequency, times/d |
|---|---|---|
| 1 | 0.625 | 3 |
| 2 | 0.625 | 3 |
| 3 | 0.625 | 4 |
| 4 | 1.25 | 2 |
| 5 | 1.25 | 3 |
| 6 | 1.25 | 3 |
| 7 | 1.25 | 3 |
| 8 | 2.5 | 3 |
| 9 | 2.5 | 3 |
| 10 | 2.5 | 3 |
| 11 | 1.25 | 3 |
| 12 | 1.25 | 2 |
| 13 | 0.625 | 2 |
| 14 | 0.625 | 2 |
| 15 | Discontinue | |

*The dose should be titrated, with anticraving and antiwithdrawal effects weighed against possible side effects. Maintenance bromocriptine treatment may be necessary if symptoms recur after discontinuation.

Various psychoactive medications have been tried in the early phase of cocaine abstinence with some success. Several studies have confirmed that dopamine plays a major role in the euphoria and rewards of cocaine use.[27,28,30] Habitual cocaine use leads to dopamine depletion, and this may cause the drug craving and other withdrawal symptoms that lead to repeated drug use.[34]

The dopamine agonist, bromocriptine mesylate, has been administered to cocaine addicts in several studies. There are rapid anticraving effects seen in open trials and double-blind placebo-controlled studies.[35-38] Several other studies have confirmed this finding.[27,31] In one report bromocriptine was found to block the cocaine-induced euphoria.[39] Bromocriptine is administered for 14 days to cocaine abusers. Treatment can continue as necessary if craving reoccurs (Table 2).

Bromocriptine actions appear to reduce the dopamine depletion and receptor density. The administration of a precursor of dopamine, tyrosine, may have limited use, as well as the replacement of vitamins involved as cofactors in catecholamine synthesis.[40,41]

Tennant and Sagherian in a double-blind study compared the use of high-dose bromocriptine and amantadine hydrochloride and found both effective in reducing the symptoms of cocaine withdrawal.[39] In another study comparing the use of bromocriptine with that of amantadine in the outpatient treatment of cocaine abuse, the initial effect of these agents was similar in decreasing cocaine craving.[31] In this preliminary study, however, the investigators found bromocriptine to have longer effects than amantadine in reducing cravings. In fact, there was no significant difference between the use of placebo and that of amantadine by day 25. Amantadine acts by releasing dopamine into the synaptic cleft. Whereas there may be an initial relief, this action may reduce already depleted dopamine stores.[31]

Khantzian has reported that methylphenidate will reduce craving in cocaine abusers who have residual attention deficit disorder.[42] Gawin and Kleber, however, studied patients who did not have attention deficit disorder and reported a transient decrease in craving with the use of methylphenidate hydrochloride, but after two weeks methylphenidate appeared to stimulate cocaine craving.[43] At best it appears methylphenidate may have limited use in the treatment of cocaine abuse, except for those persons with a residual attention deficit disorder, because of the stimulatory effects and its abuse potential.

Another dopamine agent that has been studied is a combination drug containing levodopa and carbidopa.[9] In an open study using these agents, patients reported decreased cocaine cravings.[44] Cocores and associates have reported abstinence for as long as 120 days among crack users using bromocriptine or levodopa in an outpatient setting.[45]

Several investigators have evaluated the use of tricyclic antidepressants in cocaine abuse treatment. The initial rationale was that these agents reverse the anhedonic symptoms in major depression. Antidepressants may also be of use in the withdrawal symptoms of chronic cocaine abuse because one of their actions is to block the reuptake of catecholamines and stabilize the receptor.[46]

In an open study, desipramine hydrochloride in doses of 25 to 100 mg was used, resulting in a reduction in craving.[47] Gawin in an outpatient, open clinical trial evaluated the use

of desipramine in cocaine abusers,[48] excluding patients with a diagnosis of major depression to avoid the possibility that desipramine was treating a major affective illness. Ten patients reported decreased cocaine use and craving. Other antidepressants studied include trazodone hydrochloride and imipramine hydrochloride with similar findings of reduced craving. In a placebo-controlled, double-blind study, desipramine, 75 to 100 mg, was used and no difference was found between the placebo and desipramine groups.[49] Kosten and colleagues found the same positive effects when desipramine was used by patients maintained with methadone hydrochloride who abused cocaine.[50]

A double-blind pilot study comparing desipramine and amantadine use in the treatment of cocaine dependence in methadone-maintained patients showed decreased craving in both study groups. The desipramine group, however, was more likely to remain in treatment at the end of three months. Of interest are their findings of no significant difference among the groups, including the placebo group, in abstaining from cocaine use, the amount of craving, self-reports of cocaine use, and changes in depressive symptoms.[50] The authors suggest that this is probably due to the comprehensive treatment service delivery system of cocaine abusers in a methadone maintenance program. Woody and co-workers have also shown the importance of providing psychosocial services as well as detoxification for these patients.[51] Antidepressants have demonstrated some effectiveness in decreasing cocaine cravings in some populations; this response has a lag time of 10 to 21 days.

Lithium carbonate has been used to treat cocaine abuse by decreasing craving, but this effect seems to apply only in those patients with a bipolar disorder.[52]

Because dopamine plays a prominent role in producing the euphoric effects of cocaine, there have been suggestions to look to agents that block dopamine receptors such as neuroleptic agents. A preliminary report on the use of low-dose flupentixol in crack addicts shows a decrease in cravings.[53] Flupentixol is a xanthene that reportedly has antidepressant activity at low doses and neuroleptic activity at higher doses. Although neuroleptic agents may have a beneficial effect in reducing craving, they may have limited use because of the long-term complications of tardive dyskinesia. Other drugs under investigation include calcium channel blockers.

## Treatment Issues

Cocaine addiction is a chronic, progressive, relapsing disease in which medical, psychiatric, and social deterioration occurs. Treatment should take into account the extent of addiction and the degree of deterioration in an addict's life.

Pharmacologic agents are used in both outpatient and inpatient settings. The task is to achieve abstinence, and these agents are used to promote a safe detoxification and to lessen the discomfort of withdrawal. To date there are no agents to assure abstinence. There is no "magic bullet."

When treating the addicted population, the overall medical state of a person needs a thorough evaluation to avoid unwarranted complications. This is especially true if pharmacologic agents are used; for example, the cardiovascular status needs careful evaluation if tricyclic antidepressants are used. A complete medical history, physical examination, and laboratory tests are indicated in this population because of the numerous medical complications from cocaine abuse. Anyone with signs of severe infection or of overdose—for example, severe hyperthermia, cardiac arrest, or seizures—needs aggressive medical treatment.

For many, a structured, comprehensive outpatient program using a peer support group, a 12-step program, educational sessions, family assessment, and urine monitoring to assess the program's goal of abstinence is warranted.

Cocores and Gold, in a preliminary study, compared drop-out rates of intranasal cocaine users versus freebase users in a structured outpatient setting.[54] It was found that the dropout rate in freebasers was double that of intranasal users. It appears that additional therapeutic interventions may be warranted in those using high-delivery systems that are characterized by increased concentration, a quicker onset of activity, higher peak blood levels, and shorter duration.

Indications for hospital treatment include the repeated failure of outpatient programs; concomitant medical complications; the presence of psychiatric illnesses such as psychosis or suicidal or homicidal thoughts; a concomitant dependence on other addicting substances such as sedative-hypnotic agents, where abstinence may lead to substantial morbidity such as withdrawal seizures; continued drug use in spite of concomitant medical complications such as seizures, serious infections, or cardiac disease; and the extent and degree of a patient's engagement in highly addictive methods such as long-term intravenous use or crack use.

The need for treatment in cocaine addiction is emphasized by the many medical complications as well as the family and legal complications. As an example of the legal complications, the Drug Use Forecasting program of the National Institute of Justice has released information regarding drug use among arrestees from 13 cities in a three-month period in 1989.[55] Urine specimens were collected on a voluntary basis with the exclusion of those charged with traffic offenses or vagrancy. Also, the number of participants charged with the sale or possession of drugs was 25% or less of the sample. Urine tests were positive for cocaine in 76% of male arrestees in New York, 74% in Philadelphia, 65% in Washington, DC, 59% in New Orleans, and 56% in Cleveland. The popularity of cocaine among women is evidenced by the number of female arrestees with positive urine tests: 72% in New York, 74% in Philadelphia, 73% in Washington, DC, 61% in Kansas City, and 56% in New Orleans. Multiple-drug use (alcohol was not included in the urine screens) was 30% in male arrestees in New York, Philadelphia, San Diego, and Washington, DC. Cocaine and heroin were the most frequently injected drugs, and of the current intravenous users in ten cities, more than 20% reported sharing needles.

## Conclusion

Whenever pharmacologic agents are employed in addicted patients, the primary goal is obtaining and sustaining abstinence. The use of these agents has been moderately successful in the initial phase of abstinence, but they have been more than disappointing in promoting sustained abstinence. In fact, because of the powerful positive reinforcement properties of crack and the negative reinforcement of withdrawal,[56] relapse has been more the rule than the exception. The central neurobiologic mechanisms involved in cocaine toxicity are still poorly understood. There are no cocaine antagonistic agents such as naltrexone is to heroin.

Pharmacologic agents are to be considered at best as adjuncts to a comprehensive treatment approach. Continued investigation of cocaine's psychobiologic effects is warranted.

## REFERENCES


1. Gold MS: 800-Cocaine. New York, Bantam Books, 1984

2. Peterson RC: History of Cocaine. Natl Inst Drug Abuse Res Monogr Ser 1977; 13:17-34

3. Spitz HI, Rosecan JS: Cocaine reconceptualized: Historical overview. *In* Cocaine Abuse: New Directions in Treatment and Research. New York, Brunner-Mazel, 1987, pp 5-16

4. Kleber HD: Cocaine abuse: Historical, epidemiological and psychological perspectives. J Clin Psychiatry 1988; 49(Suppl):3-6

5. Estroff TW, Gold MS: Medical and psychiatric complications of cocaine abuse. Adv Alcohol Subst Abuse 1986; 5:61-76

6. Gold MS, Verebey K: The psychopharmacology of cocaine. Psychiatr Ann 1984; 14:714-723

7. Aronson TA, Craig TS: Cocaine precipitation of panic disorder. Am J Psychiatry 1986; 143:643-645

8. Louie AK, Lannon RA, Ketter TA: Treatment of cocaine-induced panic disorder. Am J Psychiatry 1989; 146:40-44

9. Washton AM, Gold MS: Chronic cocaine abuse: Evidence for adverse effects on health and functioning. Psychiatr Ann 1984; 14:733-739

10. Dackis CA, Gold MS, Estroff TW: Inpatient treatment of addiction. *In* Karasu TB (Ed): Treatments of Psychiatric Disorders—A Task Force Report of the American Psychiatric Association, Vol 2, Washington, DC, American Psychiatric Press, 1989, pp 1359-1379

11. Nathan JA, Clark HW, Dean NC, et al: Pulmonary functions in cocaine dependent freebase smokers. Adv Alcohol Subst Abuse, in press

12. Drug Abuse Warning Network, Rockville, Md, National Institute on Drug Abuse 1988; 1:8

13. Gold MS, Ehrenkranz JRL, Ehrhart W, et al: Treatment of acute cocaine toxicity. Soc Neurosci Abstr 1988; 14:661

14. Mule SJ: The pharmacodynamics of cocaine abuse. Psychiatr Ann 1984; 14:724-727

15. Washton AM, Gold MS: Cocaine: A Clinician's Handbook. New York, Guilford Press, 1987, pp 55-72

16. Cregler LL, Herbert M: Medical complications of cocaine abuse. N Engl J Med 1986; 315:1495-1500

17. Klonoff DC, Andres BT, Obana WG: Stroke associated with cocaine use. Arch Neurol 1989; 46:989-993

18. Chaisson RE, Bacchetti P, Osmond D, et al: Cocaine use and HIV infection in intravenous drug users in San Francisco. JAMA 1989; 261:561-565

19. Novick LF, Berns D, Stricof R, et al: HIV seroprevalence in newborns in New York State. JAMA 1989; 261:1745-1750

20. Roth D, Alarcón FJ, Fernandez JA, et al: Acute rhabdomyolysis associated with cocaine intoxication. N Engl J Med 1988; 319:673-677

21. Cocores JA, Dackis CA, Gold MS: Sexual dysfunction secondary to cocaine abuse in two patients. J Clin Psychiatry 1986; 47:384-385

22. Gold MS: Sexual dysfunction challenges today's addiction clinicians. Alcohol Addict 1987; 7:11

23. Clayton RR: Cocaine use in the US. Natl Inst Drug Abuse Res Monogr Ser 1985; 61:8-34

24. Effects of crack cocaine in New York City. Washington, DC, US Dept of Justice, Drug Enforcement Administration, January 1989

25. Chasnoff IJ, Griffith DR, MacGregor S, et al: Temporal patterns of cocaine use in pregnancy. JAMA 1989; 261:1741-1744

26. Zuckerman B, Frank DA, Hingson R, et al: Effects of maternal marijuana and cocaine use on fetal growth. N Engl J Med 1989; 320:762-768

27. Dackis CA, Gold MS: The new concept in cocaine addiction: The dopamine depletion hypothesis. Neurosci Biobehav Rev 1985; 9:469-477

28. Garder EL: Brain reward, drug addiction relationship. Psychiatr Times 1989 Oct, pp 12-16

29. Dackis CA, Gold MS: Psychopharmacology of cocaine. Psychiatr Ann 1988; 18:528-530

30. Wyatt RJ, Karoum F, Suddath R: The role of dopamine in cocaine use and abuse. Psychiatr Ann 1988; 18:531-534

31. Giannini AJ, Folts DJ, Feather JN, et al: Bromocriptine and amantadine in cocaine detoxification. Psychiatr Res 1989; 29:11-16

32. Byck R, Ruskis A, Ongerer J, et al: Naloxone potentiates cocaine effect in man. Psychopharmacol Bull 1982; 18:214-215

33. Rosecan JS, Nunes EV: Pharmacological management of cocaine abuse. *In* Spitz HI, Rosecan JS (Eds): Cocaine Abuse: New Directions in Treatment and Research. New York, Brunner-Mazel, 1987, 255-270

34. Gawin FH: Chronic neuropharmacology of cocaine: Progress in pharmacotherapy. J Clin Psychiatry 1988; 49(Suppl):11-16

35. Dackis CA, Gold MS: Bromocriptine as treatment of cocaine abuse. Lancet 1985; 1:1151-1152

36. Dackis CA, Gold MS: Pharmacological approaches to cocaine addiction. J Subst Abuse Treat 1985; 2:139-145

37. Giannini AJ, Baumgartel P, DiMarzio LR: Bromocriptine therapy in cocaine withdrawal. J Clin Pharmacol 1987; 27:267-270

38. Giannini AJ, Billet W: Bromocriptine-desipramine protocol in treatment of cocaine addiction. J Clin Pharmacol 1987; 27:549-554

39. Tennant FS, Sagherian AA: Double-blind comparison of amantadine and bromocriptine for ambulatory withdrawal from cocaine dependence. Arch Intern Med 1987; 147:109-112

40. Gold MS, Pottash ALC, Annitto WJ, et al: Cocaine withdrawal: Efficacy of tyrosine. Soc Neurosci Abstr 1983; 9:157

41. Trachtenberg MC, Blum K: Improvement of cocaine-induced neuromodulator deficits by the neuronutrient tropamine. J Psychoactive Drugs 1988; 20:315-331

42. Khantzian EJ: Methylphenidate (Ritalin) treatment of cocaine dependence—A preliminary report. J Subst Abuse Treat 1984; 1:107-112

43. Gawin FH, Kleber HD: Methylphenidate treatment of cocaine abusers without ADD. Am J Drug Alcohol Abuse 1985; 11:193-197

44. Rosen H, Flemenbaum A, Slater VL: Clinical trial of carbidopa-L-dopa combination for cocaine abuse (Letter). Am J Psychiatry 1986; 143:1493

45. Cocores JA, Gold MS, Pottash ALC: Dopaminergic treatments in cocaine withdrawal. Soc Neurosci Abstr 1989; 15:251

46. Charney DS, Menkos DB, Heninger GR: Receptor sensitivity and mechanism of action of antidepressant treatment: Implications for the etiology and therapy of depression. Arch Gen Psychiatry 1981; 38:1160-1180

47. Tennant FS, Rawson RA, McCann MA: Withdrawal from chronic phencyclidine (PCP) dependence with desipramine. Am J Psychiatry 1981; 138:845-847

48. Gawin FH: New uses of antidepressants in cocaine abuse. Psychosomatics 1986; 27:s24-s29

49. Tennant FS, Tarver AL: Double-blind comparison of desipramine and placebo in withdrawal from cocaine dependence. Natl Inst Drug Abuse Res Monogr Ser 1984; 55:159-163

50. Kosten TR, Schuman B, Wright D, et al: A preliminary study of desipramine in the treatment of cocaine abuse in methadone maintenance patients. J Clin Psychiatry 1987; 48:442-444

51. Woody GE, McLellan AT, Luborsky L, et al: Psychiatric severity as a predictor of benefits from psychotherapy. Am J Psychiatry 1984; 141:1172-1177

52. Gawin FH, Kleber HD: Cocaine abuse treatment: Open pilot trial with desipramine and lithium carbonate. Arch Gen Psychiatry 1984; 41:903-909

53. Gawin FH, Allen D, Humblestone B: Outpatient treatment of 'crack' cocaine smoking with flupenthixol decanoate. Arch Gen Psychiatry 1989; 46:322-325

54. Cocores JA, Gold MS: Recidivism in Cocaine Smokers Versus Snorters. Atlanta, American Medical Society on Alcoholism and Other Drug Dependencies, 1988

55. Drug Use Forecasting, January-March, 1989. Natl Inst Justice 1989, pp 1-8

56. Gold MS: The cocaine epidemic: What are the problems, insights and treatments? Pharmacy Times 1987, pp 36-42

**Addiction Medicine**
**and the Primary Care Physician**

# Cigarette Smoking, Nicotine Dependence, and Treatment

KAREN LEA SEES, DO, *San Francisco*

*Since the 1988 Surgeon General's report on nicotine addiction, more attention is being given to nicotine dependence as a substantial contributing factor in cigarette smokers' inability to quit. Many new medications are being investigated for treating nicotine withdrawal and for assisting in long-term smoking abstinence. Medications alone probably will not be helpful; they should be used as adjuncts in comprehensive smoking abstinence programs that address not only the physical dependence on nicotine but also the psychological dependence on cigarette smoking.*

(Sees KL: Cigarette smoking, nicotine dependence, and treatment, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:578-584)

Physicians have long been frustrated in attempts to help patients stop smoking, and, until recently, they have had few tools other than advice. Cigarette smoking and other forms of tobacco consumption, however, are now acknowledged as causing nicotine dependence, and with that recognition comes the acceptance of treating tobacco use not merely as a bad habit, or nasty vice, but as the disease of nicotine addiction. The recognition that using tobacco products causes nicotine addiction helps remove the long-accepted idea that it takes only will power to stop smoking and thereby brings all treatment modalities normally used in treating other chemical dependencies into the treatment arena for nicotine addiction. In 1990 physicians have many more treatment options to offer patients who continue to smoke.

## Nicotine Addiction

The diagnosis of tobacco dependence was first added to the *Diagnostic and Statistical Manual of Mental Disorders* by the American Psychiatric Association in the 1980 third edition (DSM-III)[1]; the diagnosis was changed to nicotine dependence in the revised third edition (DSM-III-R) published in 1987.[2] In the years since this diagnosis was first introduced as a chemical dependence, not much had happened until recently to emphasize the need for treatment. This is finally starting to change.[3]

Since former Surgeon General C. Everett Koop's 1988 report, "The Health Consequences of Smoking—Nicotine Addiction,"[4] more attention is being focused on the addictive aspects of cigarette smoking and the use of other tobacco products.

If the DSM-III-R criteria for psychoactive substance use disorders are considered, it is difficult to argue that cigarette smoking does not cause addiction. All nine of these diagnostic criteria apply almost universally to cigarette smokers. In addition, according to the DSM-III-R, only three of the nine criteria need be met to make the diagnosis of psychoactive substance dependence.

*DSM-III-R Diagnostic Criteria for Psychoactive Substance Dependence*

- *Substance often taken in larger amounts or over a longer period than the person intended.*
- *Persistent desire or one or more unsuccessful efforts to cut down or control substance use.* Most cigarette smokers have tried unsuccessfully to quit in the past, and it is estimated that more than 90% of current smokers would like to quit smoking.[5]
- *A great deal of time spent in activities necessary to get the substance, taking the substance, or recovering from its effects.* Smokers spend considerable amounts of time and effort each day involved with cigarettes: making sure cigarettes are available, making sure they never run out, going out of the way to buy them, cleaning up after smoking, and actual time spent smoking, especially with chain smoking. In addition, each year cigarette smokers spend a substantial amount of time recovering from smoking-related or smoking-exacerbated illnesses.
- *Frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations at work, school, or home or when substance use is physically hazardous.* Smoking is the leading cause of fire deaths in the United States,[6] and smoking in bed is one of the leading causes of domestic fires. Certainly this constitutes "when substance use is physically hazardous."
- *Important social, occupational, or recreational activities given up or reduced because of substance use.* Fewer and fewer persons, social gathering places, workplaces, and medical care facilities tolerate smoking. Smokers, therefore, frequently limit their social activities because of where they can and cannot smoke and may choose to not work in smoke-free workplaces.
- *Continued substance use despite knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by the use of the substance.* All of the US Surgeon General's reports since 1964

From the Department of Psychiatry, University of California, San Francisco, School of Medicine, and the Substance Abuse Inpatient Unit, Veterans Administration Medical Center, San Francisco.

Reprint requests to Karen Lea Sees, DO, Assistant Chief, Substance Abuse Inpatient Unit, 116-M, VA Medical Center, 4150 Clement St, San Francisco, CA 94121.

have adjudged cigarette smoking the most important cause of preventable morbidity and premature mortality. Most cigarette smokers have experienced some smoking-related health problem, be it as simple as a prolongation of a viral syndrome or as critical as a life-threatening illness.

• *Marked tolerance: need for markedly increased amounts of the substance in order to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount.* Many smokers, when they first smoked, became sick and intoxicated after the first few puffs from the cigarette—with exposure to small amounts of nicotine. After only a few weeks of smoking, smokers can tolerate large doses of nicotine that would have been profoundly toxic on first exposure.[7] Changes in behavior, heart rate, electroencephalograms, and psychoactive tolerance develop quickly.[4]

• *Characteristic withdrawal symptoms.* Some or all of the following symptoms are frequently encountered during nicotine withdrawal: difficulty concentrating, increased appetite or hunger, tobacco craving, gastrointestinal disturbances, sleep disturbances, stress intolerance, restlessness, nervousness, drowsiness, fatigue, depression, irritability, impatience, anxiety, headache, and tension.[4] Many of the symptoms of cognitive impairment during nicotine withdrawal peak at 24 to 48 hours of abstinence. Some aspects of cognitive functioning remain substantially altered even after ten days, however, and it is unclear how long it takes for these to return to normal readings.[8] The time course for many nicotine withdrawal symptoms has not been studied.

• *Substance often taken to relieve or avoid withdrawal symptoms.* Many smokers who return to smoking after a cessation attempt attribute their relapse to some or several withdrawal symptoms.

Former Surgeon General Koop's 1988 report summarized criteria for drug addiction.[4] Addiction involves drug-reinforced behavior with patterns of drug use that are stereotypic, highly controlled, or compulsive, and that continue despite harmful effects from the drug. Drugs that produce addiction frequently have psychoactive effects that are pleasant or euphoriant. Drug-seeking behavior is common. The use of these drugs often leads to tolerance, and, therefore, an increasing amount is needed to produce the desired effect; the use of these drugs often leads to physical dependence that produces withdrawal symptoms when the drugs are discontinued. Relapse to the use of these drugs and recurrent craving for these drugs following abstinence attempts are frequent. All of these criteria apply for nicotine.

Thus, if the DSM-III-R diagnostic criteria for psychoactive substance use disorders and former Surgeon General Koop's criteria for drug addiction are accepted, it is difficult to deny that cigarette smoking produces nicotine addiction.

## Importance of Nicotine Addiction

Although reports of the health consequences of cigarette smoking began appearing in the medical literature in the 1950s, the social climate in the United States was such that the medical community for many years did not stress the importance of these problems and did not strongly confront the need to stop smoking. The substance abuse treatment community until recently has tried even harder to ignore this problem.

Cigarette smoking is recognized as the leading cause of preventable death in the United States,[9] the death rate in smokers being 30% to 80% higher than that in nonsmokers.[10] More than 350,000 deaths occurring annually in the United States can be directly attributed to cigarette smoking[4]; in contrast, the annual deaths from other drugs of abuse are as follows: alcohol, 125,000; alcohol plus another drug, 4,000; heroin, 4,000; cocaine, 2,000; and marijuana, 75. Another way of looking at these statistics is on a relative mortality base to user base. With illicit drug use, approximately 7,000 die from a user base of 5 million; with alcohol there are approximately 150,000 deaths from a user base of 100 million; cigarette smoking accounts for approximately 350,000 to 390,000 deaths from a user base of 50 million.[11] Cigarette smoking kills more than 1,000 people in the United States each day.

In the United States, estimates are that 25% of deaths from fire, 30% to 40% of deaths from coronary heart disease, 80% to 85% of deaths from lung cancer, and 80% to 90% of deaths from chronic obstructive lung disease are directly related to cigarette smoking.[6] In addition to lung cancer, the relationship between cigarette smoking and other forms of cancer is clearly established, including cancer of the mouth, larynx, pharynx, esophagus, urinary bladder, pancreas, kidney, and possibly stomach and cervix. Cigarette smoking also increases the risk of peripheral vascular disease, spontaneous pneumothorax, peptic ulcers, periodontal disease, chronic stomatitis, and chronic laryngitis. An increased incidence of respiratory tract and ear infections, especially in children of parents who smoke, and an exacerbation of symptoms of asthma and hypertension are also well documented.[6,10,12] Studies linking medical complications to cigarette smoke are impressive not only for the active smoker but also for the passive smoker.[13]

Several additional alarming consequences exist for women smokers. Women who smoke and use oral contraceptives are at dramatically increased risk for heart attacks, strokes, and thromboembolic events. This is particularly important because oral contraception continues to be supported as a rational means of birth control. Women who smoke during pregnancy not only increase their own risk, with a higher incidence of placenta previa, abruptio placentae, and premature birth, but they also place their unborn child at risk with these complications. Cigarette smoking during pregnancy is directly related to a higher rate of spontaneous abortions, fetal death, and neonatal death. Furthermore, babies born to smoking mothers may have impaired intellectual development and tend to be small for gestational age.[6,10,12] Unfortunately, all the implications of a woman smoking during pregnancy are not known.

In 1985 the direct health care costs of smoking-related illnesses exceeded $16 billion annually; the indirect smoking-related cost, if lost productivity and earnings from excess morbidity, disability, and premature death are considered, totaled more than $37 billion.[6] In 1988 it was estimated that a typical employer incurred at least $1,000 in excess expense per smoking employee per year compared with that for an otherwise similar nonsmoking employee.[14] Because of inflation, these costs continue to rise.

These statistics should be even more alarming for the substance abuse treatment community. Approximately a third of the adult population in the United States smokes[15]; the smoking rate in alcoholics is 90% or greater,[16,17] placing this population at a far higher risk of encountering one or

more of these unfortunate consequences. Furthermore, concomitant alcohol consumption and cigarette smoking greatly increase the risk of oral, pharyngeal, laryngeal, and esophageal cancer.[18,19] Blot and colleagues have reported a 35-fold increase in the rate of oropharyngeal cancer in men who were both heavy cigarette smokers and heavy alcohol drinkers compared with nonsmoking men who rarely drank.[18] They estimate approximately 75% of all cases of oropharyngeal cancer in the United States can be attributed directly to the simultaneous use of cigarettes and alcohol.

### Nicotine Addiction and the Substance Abuse Treatment Community

Although many of the detrimental health consequences of cigarette smoking are clearly established, and cigarette smoking is now recognized as causing nicotine dependence, the substance abuse treatment community, to a large degree, continues to minimize the importance of cigarette smoking. Treatment specialists resist the need to treat cigarette smoking as an addiction, and smoking is frequently condoned. In the past, if smoking cessation was mentioned at all during drug abuse treatment, it was simply as a passing comment that no patient should attempt to quit smoking until sometime in the future, after the primary addiction had stabilized. Many treatment specialists even put a time line on this, telling patients to wait until they have been sober at least a year before thinking about stopping smoking. If patients expressed a specific interest in smoking cessation during drug treatment, they were usually overtly discouraged.

The dogma in the substance abuse treatment community was and to a large extent continues to be that it is too difficult to give up all addictions at the same time. The contention was that an alcoholic or cocaine addict who had attempted and failed to quit smoking was subsequently at a higher risk to relapse to the primary addiction and that even after years of sobriety from the drug of choice, attempting smoking cessation might put the recovering addict or alcoholic at an increased risk of relapse. Bobo and Gilchrist reported the results of a survey of 311 alcoholism treatment professionals and found that 23% would never encourage an alcoholic client to quit smoking, even after five years of abstaining from alcohol.[20] In this study, alcoholism treatment professionals who thus responded were most likely to be recovering alcoholics who continued to smoke. Although this survey was done several years ago, to a large extent these notions continue to the present day, but treatment specialists are beginning to question this conventional wisdom.

The limited research available suggests that abstinent alcoholics, even those with extensive substance abuse histories, can successfully stop smoking without relapsing to alcohol or jeopardizing their sobriety.[21] In addition, alcoholics who successfully stop smoking are more likely to maintain long-term abstinence from alcohol.[17] To date no research has been reported on the relationship between abstaining from other psychoactive drugs of abuse and abstaining from smoking.

Data indicate that when an alcoholic has stopped smoking and drinking and subsequently returns to drinking, he or she almost always also returns to smoking; the relapse rate to alcohol after first returning to smoking is essentially the same as the relapse rate for alcoholics in general.[22] Although there is only a small amount of research done on this topic, it indicates that relapsing first to alcohol increases the relapse rate to cigarettes, but relapsing first to cigarettes does not increase the relapse rate to alcohol.

A few chemical dependence treatment programs are pioneering addressing nicotine dependence concurrently with the treatment of the primary drug (M. Branch, J. Knapp, K. Berntson, "Minneapolis Veterans Hospital Goes Smoke-Free," *Countdown*, 1988; 3:1-7).[17,23,24] Just as they refuse to ignore social drinking of alcohol in cocaine users or occasional marijuana use in alcoholics, they are putting the emphasis on a psychoactive drug-free status—including nicotine. Anecdotal reports are encouraging, but rigorous outcome studies are needed.

Survey results of smoking in Minnesota's substance abuse treatment units revealed that 72% of the program directors thought nicotine dependence should be treated as an addiction; only 11% had nicotine treatment as a part of their chemical dependence treatment program, however. Although 41% thought tobacco treatment should be offered after the treatment of other drug abuse, 31% thought it should be done concurrently with other drug abuse treatment, and 26% were not sure.[25]

Obstacles are frequently encountered in treating nicotine addiction simultaneously with other forms of chemical dependence or in making a chemical dependence treatment unit smoke-free, or both. Those most often noted include the following:

- Fear of jeopardizing the progress of recovery from other forms of chemical dependence;
- Financial concerns about losing patients to treatment programs that do not address nicotine dependence;
- Concern about reimbursement from insurance companies or from patients;
- Resistance to change because historically smoking cessation programs have developed outside of traditional medical settings;
- Worry about being in competition with already established smoking cessation programs;
- Speculation that it will be a problem for patients to abstain from nicotine during involvement in 12-step programs;
- A lack of research regarding when to treat nicotine addiction;
- A lack of research regarding how to treat nicotine dependence—Should it be voluntary or mandatory? Is there a need for pharmacologic detoxification? What medication should be used? Are special groups needed, or will generic substance abuse groups suffice?
- Concerns about intruding on individual rights of the patients and staff;
- Concerns about enforcing the smoking policy; and
- Continued abuse of and dependence on nicotine by treatment staff.[17,24,26]

All of these obstacles must be overcome. Although cigarette smoking is now readily accepted as causing nicotine dependence, the notion that nicotine addiction pales in comparison with other drug addictions like cocaine, heroin, and alcohol persists. Hand in hand with that notion is the belief that nicotine addiction should not be addressed concurrently with other addictions. The reluctance by the substance abuse treatment community to accept cigarette smoking as a serious life-threatening addiction and to aggressively treat nicotine addiction is appalling. The question should not be

whether to treat nicotine addiction, but when and how to treat nicotine addiction.[24,27] Research is needed to answer the many questions that arise.

## Treating Nicotine Addiction

A physician has to do more than offer patients the good advice to stop smoking, although mere advice from a physician to quit smoking does increase the number of patients who successfully stop smoking, with the one-year abstinence rate increasing from 0.3% with no advice to 3.3% to 5.1% when advice is given.[28] These percentages are small, but this research is notable in that it reinforces the idea that even in a busy physician's office, a few minutes of advice can substantially affect a patient's motivation to quit smoking. When a physician can link this advice to a patient's health problem that is caused or exacerbated by smoking, the abstinence rate may increase to as high as 24% to 39% one year later.[28] There is a positive correlation between a patient's severity of illness and adherence to a physician's advice to stop smoking.[29] Unfortunately, many smokers have never been advised by their physician to stop smoking,[30] although an analysis of such physician's advice has shown that it is cost-effective even if it helps only 1% of smokers to quit.[31] Therefore, at a minimum, a physician should continue to advise all patients who are smokers to quit and make an attempt to link any health complaint to the cigarette smoking.

### *Pharmacologic Adjuncts for Nicotine Withdrawal*

It has been asserted that most smokers who are quitting are less dependent on nicotine.[32] Consequently, those who remain smokers today and in the future increasingly will be those who are physiologically addicted to nicotine.[33,34]

As smokers recognize the importance of the psychoactive effects of nicotine in their continuing to smoke and the importance of the nicotine withdrawal symptoms in their relapse to smoking when attempting abstinence, their requests for medical adjuncts to assist in nicotine withdrawal will increase as they attempt once again to quit smoking. As a result, physiologic interventions should play a larger role in the effort to stop smoking. For greatest efficacy, these interventions need to be used in conjunction with a comprehensive treatment strategy.

Pharmacologic adjuncts for nicotine withdrawal fall into four categories of medications: nicotine replacement therapy, which involves providing nicotine maintenance through a less hazardous means of nicotine delivery and a more manageable form of the drug; blockade therapy, which involves an antagonist medication that blocks the effects of nicotine; deterrent therapy, which produces aversive effects when triggered by cigarette smoke; and nonspecific supportive or symptomatic therapy, which attempts to alleviate the craving and symptoms of nicotine withdrawal.[7,35]

*Nicotine replacement therapy.* Nicotine replacement therapy was introduced in the United States in 1984. Its use is based on the idea that it is too difficult to simultaneously give up both the psychological dependence on cigarette smoking and the physical dependence on nicotine. Consequently, with nicotine replacement, a patient initially concentrates on the psychological aspects of smoking cessation and at a later date addresses the physical dependence by weaning off the nicotine replacement.

Nicotine gum, or nicotine polacrilex, was the first pharmacologic therapy proved to aid in smoking cessation.[36] Chewing nicotine gum attenuates or completely abolishes some nicotine withdrawal symptoms, most notably the persistent irritability, but also frequently reduces the hunger, anxiety, annoyance, hostility, restlessness, difficulty in concentrating, depression, and other somatic complaints.[4]

Nicotine gum has been useful in smoking cessation programs, but several problems with its use exist. Chewing nicotine gum does not decrease the urge to smoke.[4] The efficacy of nicotine gum diminishes considerably when simply dispensed by a physician with nothing or little else done to support smoking abstinence.[4,35,37] Nicotine gum is not well tolerated by some patients and is frequently misused, in large part because physicians do not properly instruct their patients. Patients should not be given a prescription for nicotine gum without also being given detailed instructions concerning its proper use. They should not simply be told to read the package insert on how to chew the gum. Most patients assume they know how to chew gum and do not read it.

Instructions for using nicotine gum should include the following:

- It is not to be chewed like regular chewing gum; it should be chewed slowly and intermittently;
- It takes approximately 15 chews to release the nicotine from the polacrilex; at that time a tingling sensation will be felt in the mouth;
- When the tingling sensation starts, the gum should be parked between the cheek and teeth or gums;
- When the tingling is almost gone, chewing should begin again;
- One piece of nicotine gum should be chewed for no longer than 20 to 30 minutes, and after that time period it should be discarded for another piece;
- Do not swallow immediately; 70% of the nicotine in swallowed saliva is inactivated by first-pass metabolism in the liver, and patients get minimal effect from the gum if most or all of the nicotine is swallowed; the nicotine must be absorbed in the mouth to be effective. Also, swallowing the nicotine increases the amount of nausea and potential vomiting;
- Nicotine gum should be used in sufficient quantities—usually 10 to 15 pieces per day for the average smoker, but as many as 30 may be used;
- It should be used steadily day to day, not 2 pieces today, 20 tomorrow, and 7 the next day;
- It should be used for the relief of discomfort as well as for urges to smoke;
- Avoid drinking liquids when chewing or when about to chew the gum because most liquids change the pH in the mouth, which will decrease nicotine absorption;
- Nicotine gum should be weaned gradually after a three- to six-month maintenance period.

Table 1 lists brief instructions and several recommended exclusion criteria for the use of nicotine gum.

Other nicotine replacement therapies presently under investigation include a nicotine transdermal patch,[38] a nicotine vapor inhaler, a nicotine nasal spray,[39] a roll-on tobacco extract applicator,[40] some chewable food products, and a toothpaste-like formulation.[4] At this time nicotine gum is the only nicotine replacement product with approval by the Food and Drug Administration for the treatment of nicotine withdrawal.

A concern with nicotine replacement is that one form of

TABLE 1—*Nicotine Gum*

| *Proper Use* | *Exclusion Criteria* |
|---|---|
| Chew slowly | Active temporomandibular joint disease |
| Chew intermittently | Postmyocardial infarction |
| About 15 chews to release | Serious cardiac dysrhythmias |
| Park the gum | Systemic hypertension |
| One piece lasts 20-30 minutes | Vasospastic disease |
| Do not swallow immediately | Active peptic ulcer disease |
| Use enough | Active esophagitis |
| Use steadily | Oral or pharyngeal inflammation |
| Use for relief of discomfort | Pheochromocytoma |
| Use for urges to smoke | Hyperthyroidism |
| Avoid drinking liquids | Pregnancy |
| Gradually wean | Lactation |
| | Insulin-dependent diabetes mellitus* |
| | Extensive dental work* |

*Although not absolute exclusion criteria, exercise caution when prescribing nicotine gum for these patients.

nicotine dependence is being substituted for another. Some patients have difficulty weaning off nicotine gum after the recommended period of use of three to six months. In addition, there is some evidence that the use of nicotine polacrilex is being abused by people other than those initially dependent on tobacco-delivered nicotine (H.W. Clark, MD, oral communication, 1989). More abuse of nicotine gum probably is not occurring in part owing to the amount of work, or chewing, it takes to extract the nicotine from the gum resin and the relatively unpleasant taste of the gum. As these inconveniences are eliminated, however, the potential for the abuse of nicotine delivery products increases.

*Alternatives to nicotine replacement.* Several non-nicotine medications are presently being investigated as adjuncts in smoking cessation programs. The nicotine antagonist mecamylamine hydrochloride may prove helpful, in the same way naltrexone hydrochloride is for opioid addicts, by attenuating or completely blocking the subjective effects of nicotine.[41] The major obstacle in its use for smoking cessation treatment is its anticholinergic and antihypertensive effects; it also does nothing for the conditioned and non-nicotine-mediated reinforcers from cigarette smoking.[7] A citric acid aerosol inhaler is being studied at the University of California, Los Angeles; when used it appears to satisfy the momentary urge to smoke (S. Blakeslee, "New Drug Therapies Are Being Tested to Help Smokers Quit." *New York Times,* June 9, 1988, p B6). Silver acetate has been formulated into several products as a smoking deterrent, including a chewing gum and lozenge; the exposure of silver acetate to cigarette smoke causes an unpleasant taste in the mouth. These products are complicated by the possible development of argyria, silver poisoning, with prolonged use.[42] A small study has investigated the use of naloxone hydrochloride in smoking cessation. This opioid antagonist, which is sometimes used as an adjunct in maintaining opioid abstinence, reduced the desire to smoke and actual smoking.[43] Naloxone's usefulness in smoking cessation will probably be limited by its numerous side effects, most notably lethargy, mild dysphoria, and gastrointestinal disturbances. Several over-the-counter smoking cessation preparations contain lobeline, a partial nicotinic receptor agonist, which has been found to be no more effective than placebo.[35,44]

Glassman and co-workers found that a history of depression was unexpectedly common in cigarette smokers.[45] Since their findings were reported, several investigators have looked at antidepressant and antianxiety medications as adjuncts to smoking cessation. A relatively new antidepressant, fluoxetine hydrochloride, which is a serotonin reuptake blocker, reportedly decreases the desire to smoke.[33] Although not yet reported in the medical literature, some clinical trials that have been completed have studied the efficacy of fluoxetine in promoting nicotine abstinence. Doxepin hydrochloride is under investigation at the University of Tennessee, and although the initial results are promising, a side effect of weight gain may limit this product's usefulness because many patients are already concerned about the normal weight gain associated with stopping smoking.[46] A small, open, uncontrolled clinical trial has looked at buspirone hydrochloride, an antianxiety agent that appears to decrease craving, anxiety, fatigue, and the weight gain that frequently accompany smoking cessation.[47] Buspirone is now being investigated alone and in combination with clonidine hydrochloride for treating nicotine withdrawal.

Recently clonidine has been given a great deal of attention. It is an $\alpha_2$-noradrenergic agonist that was first used as a medication to treat hypertension and has gained widespread recognition for its usefulness in treating many of the signs and symptoms of both opioid and alcohol withdrawal.[48-53] In the past five years, several studies have supported clonidine's usefulness in diminishing cigarette craving and the nicotine withdrawal symptoms of anxiety, tension, irritability, and restlessness.[46,54-56]

Clonidine has potentially serious side effects, and several exclusion criteria must be observed, including hypotension, hypersensitivity to tape (if the transdermal patch is used), hypersensitivity to clonidine, the concurrent use of amitriptyline medications, a history of auditory hallucinations or delirium, notable liver disease, pregnancy, lactation, current heavy alcohol consumption, Sjögren's syndrome, cerebrovascular disease, severe coronary artery insufficiency, a recent myocardial infarction, chronic renal failure, a patient younger than 12 years, and surgical procedures planned during the period of clonidine treatment or within a week of stopping clonidine treatment.[57]

In addition to these exclusion criteria, there are side effects to the use of clonidine that may limit its usefulness. Those most frequently noted include postural hypotension causing lightheadedness and dizziness, dry mouth, tiredness, and lethargy. Rarely, sexual dysfunction occurs. These side effects decrease or may not occur when the transdermal patch form of the medication is used in place of oral medication.[58-61]

The transdermal form of clonidine has several other advantages, including a therapeutic steady-state drug level, with only once-a-week dosing. This improves patient compliance and is less disruptive to participation in a drug treatment program by decreasing drug-seeking behavior.[49] Transdermal clonidine has a gradual onset of action that decreases the chance of precipitously lowering the blood pressure, and once removed it is an essentially self-tapering medication that may help prevent rebound hypertension.[58,62]

Many questions remain unanswered about the dose of clonidine needed, the length of time to continue the medication, the differences between men and women taking clonidine, and what effect depression has on treatment.

Franks and colleagues recently reported the results of a study that disputes clonidine's effectiveness an an adjunct in stopping smoking.[63] This clinical trial used clonidine in a primary care setting as essentially the sole therapy for quitting smoking. This setting consisted of dispensing the medication, giving the advice to stop smoking, encouraging patients to read a booklet on quitting smoking, briefly reviewing triggers to smoking and coping techniques, and evaluating weekly to ensure the patients continued to be medically stable. Just as nicotine gum has questionable effectiveness when used without being part of a comprehensive stop smoking program, so may clonidine.

A unique physiologic intervention for nicotine dependence was developed at the Haight-Ashbury Free Medical Clinic's Drug Detoxification, Rehabilitation, and Aftercare Project in San Francisco.[64] This approach combines both a rapidly decreasing dose of a nicotine replacement (nicotine gum) and a medication for the symptomatic treatment of nicotine withdrawal symptoms (transdermal clonidine). The rate of nicotine withdrawal can be controlled by the amount of the nicotine polacrilex used in 24 hours, and the withdrawal symptoms can be controlled with the dose of the transdermal clonidine. The doses of both of these medications can be adjusted. Nicotine detoxification is thereby accomplished effectively and comfortably, not unlike using clonidine as an adjunct at the end of a methadone detoxification for opioid addiction. To be most effective, this technique for nicotine withdrawal should be used as an adjunct to a comprehensive smoking cessation program.

Further research on all of these pharmaceutical adjuncts for nicotine withdrawal and abstinence is needed.

### *Nonpharmacologic Therapy for Smoking Abstinence*

In the past six years much searching has been done for the "cure" or "quick fix" for smokers who want to quit. The correlation between the success rate of simply assisting nicotine withdrawal and maintaining long-term cigarette abstinence is not known. Speculation based on other types of chemical dependence can be made, however. Detoxification from alcohol is easily and comfortably accomplished with the use of either benzodiazepines or barbiturates, but these medications for treating withdrawal symptoms do nothing to assist an alcoholic in maintaining long-term sobriety. Detoxification from opioids is easily and comfortably accomplished with either clonidine, methadone, or a combination of the two. Managing withdrawal symptoms has little to do with keeping the opioid addict from using again, however. Likewise, pharmaceutical adjuncts that may assist in nicotine withdrawal can be expected to do little for assisting an ex-smoker from relapsing to cigarettes. Simple detoxification is the easy part; remaining abstinent is more difficult.

Glassman and co-workers noted,

> Smokers may continue to smoke primarily because they derive positive effects from smoking and not because they experience withdrawal symptoms when they attempt to stop.[45(p2863)]

Just as alcoholism and other forms of chemical dependence are relapsing diseases, so is nicotine dependence. Quitting smoking is rarely a one-time proposition. It is estimated that more than 80% of smokers fail to quit on the first attempt, and even after seven attempts, more than half return to smoking.[65] It is, therefore, ideal for physicians to have additional resources to support smoking abstinence or to know what community services and programs are available for patients who are interested in stopping smoking. Some communities have Smokers Anonymous meetings that are modeled on Alcoholics Anonymous. These meetings are free and open to anyone who is interested in stopping smoking. In many areas, the American Lung Association and the American Cancer Society sponsor stop-smoking programs. More information on the availability of these programs can be obtained from local offices of these organizations. Gritz has compiled an excellent list of resources available to physicians and other health professionals on smoking cessation.[29] Stress management, coping skills, relaxation, relapse prevention training, weight management, leisure planning, contingency contracting, hypnosis, acupuncture, and social support groups are all helpful to some smokers who are trying to quit.[4]

Smoking cessation programs traditionally have dealt with the psychological and overlearned behavioral aspects of cigarette smoking. Behavioral, cognitive, psychodynamic, and peer support treatments of nicotine addiction will continue to play a primary role in smoking abstinence successes. There are now several treatment options available for patients who smoke. Physician advice that helps to motivate patients and medications that assist with nicotine withdrawal are usually not enough, however; they are only adjuncts in a comprehensive smoking abstinence program.

#### REFERENCES


1. Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed. Washington, DC, American Psychiatric Association, 1980
2. Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed Revised. Washington, DC, American Psychiatric Association, 1987
3. Sees KL: Editor's introduction: Tobacco smoking—Clinical and social issues. J Psychoactive Drugs 1989; 21:277-279
4. The Health Consequences of Smoking—Nicotine Addiction: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services, 1988
5. Fielding JE: Smoking: Health effects and control (Part 2). N Engl J Med 1985; 313:555-561
6. Fielding JE: Smoking: Health effects and control (Part 1). N Engl J Med 1985; 313:491-498
7. Jarvik ME, Henningfield JE: Pharmacological treatment of tobacco dependence. Pharmacol Biochem Behav 1988; 30:279-294
8. Snyder FR, Davis FC, Henningfield JE: The tobacco withdrawal syndrome: Performance decrements assessed on a computerized test battery. Drug Alcohol Depend 1989; 23:259-266
9. Slade J: Learning to fight *Nicotiana tabacum*. NJ Med 1988; 85:102-106
10. Holbrook JB: Tobacco smoking, *In* Petersdorf RG, Adams RD, Braunwald E, et al (Eds): Harrison's Principles of Internal Medicine. New York, McGraw-Hill, 1983
11. Blum A: Tobacco promotion and sports. American Medical Society on Alcoholism and Other Drug Dependencies. Presented at the Second National Conference on Nicotine Dependence, Chicago, September 1989
12. Burns DM: Tobacco and health, chap 11, *In* Wyngaarden JB, Smith LH (Eds): Cecil Textbook of Medicine, 18th Ed Philadelphia, WB Saunders, 1988, pp 36-40
13. Meinert LA: Scientific basis for workplace clean air. NJ Med 1988; 85:141-142
14. Kristein MM: Economic issues related to smoking in the workplace. NY State J Med 1989; 89:44-47
15. Fiore MC, Novotny TE, Pierce JP, et al: Trends in cigarette smoking in the United States—The changing influence of gender and race. JAMA 1989; 261:49-55
16. Wallace J: Smoke gets in our eyes: Professional denial of smoking. J Subst Abuse Treat 1986; 3:67-68
17. Bobo JK: Nicotine dependence and alcoholism epidemiology and treatment. J Psychoactive Drugs 1989; 21:323-329
18. Blot WJ, McLaughlin JK, Winn DM, et al: Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988; 48:3282-3287
19. Tuyns AJ, Estève J, Raymond L, et al: Cancer of the larynx/hypopharynx, tobacco and alcohol: IARC international case-control study in Turin and Varese (Italy), Zaragoza and Navarra (Spain), Geneva (Switzerland) and Calvados (France). Int J Cancer 1988; 41:483-491
20. Bobo JK, Gilchrist LD: Urging the alcoholic client to quit smoking cigarettes. Addict Behav 1983; 8:297-305
21. Bobo JK, Schilling RF, Gilchrist LD, et al: The double triumph: Sustained sobriety and successful cigarette smoking cessation. J Subst Abuse Treat 1986; 3:21-25
22. Bobo JK: Treatment of nicotine dependence and alcoholism: Is smoking cessation a threat to sobriety? American Medical Society on Alcoholism and Other Drug Dependencies, Presented at the First National Conference on Nicotine Dependence, Minneapolis, September 1988
23. Delaney GO: Tobacco dependence in treating alcoholism. NJ Med 1988; 85:131-132

24. Goldsmith RJ: Development of smoke-free chemical dependency units. American Medical Society on Alcoholism and Other Drug Dependencies. Presented at the Second National Conference on Nicotine Dependence, Chicago, September 1989

25. Knapp JM: Smoking in Minnesota's chemical dependency facilities: Survey results. American Medical Society on Alcoholism and Other Drug Dependencies. Presented at the Second National Conference on Nicotine Dependence, Chicago, September 1989

26. Donnelly RJ: Obstacles to the provision of nicotine dependence counseling to chemically dependent patients. American Medical Society on Alcoholism and Other Drug Dependencies. Presented at the Second National Conference on Nicotine Dependence, Chicago, September 1989

27. Battjes RJ: Smoking as an issue in alcohol and drug abuse treatment. Addict Behav 1988; 13:225-230

28. Philips BU, Longoria JM, Calhoun KH, et al: Behavioral prescription writing in smoking cessation counseling: A new use for a familiar tool. South Med J 1989; 82:946-953

29. Gritz ER: Cigarette smoking: The need for action by health professionals. CA 1988; 38:194-212

30. Anda RF, Remington PL, Sienko DG, et al: Are physicians advising smokers to quit? The patient's perspective. JAMA 1987; 257:1916-1919

31. Cummings SR, Rubin SM, Oster G: The cost-effectiveness of counseling smokers to quit. JAMA 1989; 261:75-79

32. Modification of Smoking Behavior, *In* Smoking and Health—A Report of the Surgeon General. Washington DC, US Dept of Health, Education, and Welfare 1979

33. Hughes JR: Clonidine, depression, and smoking cessation. JAMA 1988; 259:2901-2902

34. Hughes JR, Gust SW, Pechacek TF: Prevalence of tobacco dependence and withdrawal. Am J Psychiatry 1987; 144:205-208

35. Prignot J: Pharmacologic approach to smoking cessation. Eur Respir J 1989; 2:550-560

36. Hughes JR, Miller S: Nicotine gum to help stop smoking. JAMA 1984; 252:2855-2858

37. Lam W, Sze PC, Sacks HS, et al: Meta-analysis of randomised controlled trials of nicotine chewing-gum. Lancet 1987; 2:27-30

38. Rose JE, Herskovic JE, Trilling Y, et al: Transdermal nicotine reduces cigarette craving and nicotine preference. Clin Pharmacol Ther 1985; 38:450-456

39. Jarvis MJ, Hajek P, Russell MAH, et al: Nasal nicotine solution as aid to cigarette withdrawal: A pilot clinical trial. Br J Addict 1987; 82:983-988

40. Allen DW: Transdermal tobacco extract reduces reported cigarette consumption. Med J Aust 1988; 149:342

41. Stolerman IP: Could nicotine antagonists be used in smoking cessation? Br J Addict 1986; 81:47-53

42. Jensen EJ, Rungby J, Hansen JC, et al: Serum concentrations and accumulation of silver in skin during three months' treatment with an anti-smoking chewing gum containing silver acetate. Hum Toxicol 1988; 7:535-540

43. Karras A, Kane JM: Naloxone reduces cigarette smoking. Life Sci 1980; 27:1541-1545

44. Henningfield J: Neuropharmacology of nicotine. American Medical Society on Alcoholism and Other Drug Dependencies. Presented at the Second National Conference on Nicotine Dependence, Chicago, September 1989

45. Glassman AH, Stetner F, Walsh T, et al: Heavy smokers, smoking cessation, and clonidine. JAMA 1988; 259:2863-2866

46. Edwards NB, Murphy JK, Downs AD, et al: Doxepin as an adjunct to smoking cessation: A double-blind pilot study. Am J Psychiatry 1989; 146:373-376

47. Gawin F, Compton M, Byck R: Buspirone reduces smoking. Arch Gen Psychiatry 1989; 46:288-289

48. Baumgartner GR, Rowen RC: Clonidine vs. chlordiazepoxide in the management of acute alcohol withdrawal syndrome. Arch Intern Med 1987; 147:1223-1226

49. Clark HW, Longmuir N: Clonidine transdermal patches: A recovery oriented treatment of opiate withdrawal. Calif Soc Treat Alcohol Other Drug Depend News 1986; 13:1-2

50. Mahem P, Nilsson LH, Moberg A, et al: Alcohol withdrawal: Effects of clonidine treatment on sympathetic activity, the renin-aldosterone system, and clinical symptoms. Alcohol Clin Exp Res 1985; 9:238-243

51. Walinder J, Balldin J, Bokstrom K, et al: Clonidine suppression of the alcohol withdrawal syndrome. Drug Alcohol Depend 1981; 8:345-348

52. Gold MS, Pottash AC, Sweeney DR, et al: Opiate withdrawal using clonidine. JAMA 1980; 243:343-346

53. Gold MS, Redmond DE Jr, Kleber HD: Clonidine in opiate withdrawal (Letter). Lancet 1978; 1:929-930

54. Glassman AH, Jackson WK, Walsh BT, et al: Cigarette craving, smoking withdrawal, and clonidine. Science 1984; 226:864-866

55. Appel D: Clonidine helps smokers stop smoking. Am Rev Respir Dis Suppl 1987; 135:A354

56. Ornish SA, Zisook S, McAdams LA: Effects of transdermal clonidine treatment on withdrawal symptoms associated with smoking cessation. Arch Intern Med 1988; 148:2027-2031

57. Sees KL, Clark HW: Clonidine use in nicotine withdrawal. J Psychoactive Drugs 1988; 20:263-268

58. Josse S, Danays T, Lafferre M, et al: Substitution of oral clonidine with transdermal clonidine in hypertensive patients. Curr Ther Res 1987; 42:579-584

59. Burris JF, Mroczek WJ: Transdermal administration of clonidine: A new approach to antihypertensive therapy. Pharmacotherapy 1986; 6:30-34

60. Hollifield J: Clinical acceptability of transdermal clonidine: A large-scale evaluation by practitioners. Am Heart J 1986; 112:900-906

61. Weber MA: Clinical experience with transdermal antihypertensive therapy. Pract Cardiol 1986; 12:104-120

62. Lowenthal DT, Saris S, Paran E, et al: Efficacy of clonidine as transdermal therapeutic system: The international clinical trial experience. Am Heart J 1985; 112:893-900

63. Franks R, Harp J, Bell B: Randomized, controlled trial of clonidine for smoking cessation in a primary care setting. JAMA 1989; 262:3011-3013

64. Sees KL, Stalcup SA: Combining clonidine and Nicorette for treatment of nicotine withdrawal. J Psychoactive Drugs 1989; 21:355-359

65. The Health Consequences of Smoking—Chronic Obstructive Lung Disease: A Report of the Surgeon General. Washington DC, US Dept of Health and Human Services, 1984

Addiction Medicine
and the Primary Care Physician

# Expert Systems in Treating Substance Abuse

DONALD R. WESSON, MD, *San Francisco, and* ROBERT H. HINK, PhD, *Berkeley, California*

*Computer programs can assist humans in solving complex problems that cannot be solved by traditional computational techniques using mathematic formulas. These programs, or "expert systems," are commonly used in finance, engineering, and computer design. Although not routinely used in medicine at present, medical expert systems have been developed to assist physicians in solving many kinds of medical problems that traditionally require consultation from a physician specialist. No expert systems are available specifically for drug abuse treatment, but at least one is under development. Where access to a physician specialist in substance abuse is not available for consultation, this expert system will extend specialized substance abuse treatment expertise to nonspecialists. Medical expert systems are a developing technologic tool that can assist physicians in practicing better medicine.*

(Wesson DR, Hink RF: Expert systems in treating substance abuse, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:585-587)

An "expert system" is a specialized computer program that assists humans in solving difficult problems. Unlike a computer program that solves complex problems using mathematic equations, expert systems solve problems that cannot be reduced to precise mathematic formulas. In its problem-solving approach, an expert system emulates that of a human expert in some limited domain, such as an area of expertise. Like the human expert, an expert system processes information by applying general rules, sometimes called heuristics, to arrive at a recommended solution to a problem.

Expert systems have been developed to solve problems in finance, oil exploration, computer design, and medicine. Table 1 lists some of the medical expert systems that are available.

As in other areas of medicine, many problems in substance abuse treatment lend themselves to the expert system approach; however, no expert systems have been developed specifically to assist physicians in substance abuse treatment.

With grant support from the National Institute on Drug Abuse, we are developing an expert system to assist physicians in the detoxification process for patients who are withdrawing from drugs of abuse. This expert system, called DETOX, can be run by physicians on microcomputers to aid them in planning detoxification schedules. The development of this system was inspired by the following incident:

The patient, a 35-year-old woman admitted to an inpatient chemical dependence treatment program, had been ingesting 6 to 10 tablets of Fiorinal with Codeine* per day for 4 years before admission. The admitting physician wrote detoxification orders for the codeine but did not write sedative-hypnotic detoxification orders because he did not know that each Fiorinal tablet contains 50 mg of butalbital. As a result, the patient had a barbiturate withdrawal seizure on the second hospital day.

*Fiorinal with Codeine is a combination product containing codeine phosphate, butalbital, caffeine, and aspirin.

This case example illustrates one reason why an expert system for detoxification would be useful. No physician can possibly know the ingredients of all prescription medications. Improperly treated during withdrawal, a patient who is physically dependent on sedative-hypnotic agents may have major motor seizures or psychosis with abrupt withdrawal. Uncontrolled withdrawal from alcohol and some other sedative-hypnotics can be fatal. Yet, many prescription and street drugs contain sedative-hypnotics. Because an expert system can supply more information than any physician can possibly recall and can check that all pertinent information is considered, it can assist a physician in identifying medications containing sedative-hypnotics or street drugs and to arrive at the best clinical decision regarding detoxification.

Drug users are often treated by primary care physicians who do not specialize in treating drug abuse. Where a physician specialist in substance abuse cannot be readily consulted, expert systems provide a means of extending specialized expertise to nonspecialist physicians. Making detoxification more efficient can shorten inpatient treatment and lower the cost of treatment, an important consideration in an era of medical cost containment.

## Expert Systems Versus Decision Support Systems

Expert systems are an extension of more traditional programs that physicians may use for decision support. A decision support system provides information. An example that might be familiar to many physicians is PDR (Medical Economics Company, Inc, Oradell, NJ), a microcomputer program that gives electronic access to drug interactions and side effects. The program is essentially an electronic *Physicians Desk Reference.* The program is a good example of a decision support program.

From the Department of Psychiatry, University of California, San Francisco, School of Medicine, and Veterans Administration Medical Center, San Francisco, and the Research Department, Merritt Peralta Institute, Oakland (Dr Wesson), and Expert System Designs, Inc, Berkeley, California (Dr Hink).

Reprint requests to Donald R. Wesson, MD, Merritt Peralta Institute, 435 Hawthorne Ave, Oakland, CA 94609.

An expert system also gives access to information, but it does more; it gives access to knowledge—relationships between facts and desired goals. This distinction between knowledge and information is crucial to understanding what expert systems offer that decision support systems do not. If a person wished to know the number of cities in the United States with populations greater than 10 million, he or she might consult an almanac, a source of facts or information. On the other hand, to determine the best route to drive from Los Angeles to New York City, a person would probably refer to a road map, a source of knowledge for solving specific kinds of problems. In this case the problems would be finding the best route from point A to point B, where "best" might mean shortest, quickest, most scenic, safest, or some combination.

A decision support system could scan a data base containing records of cities in the United States and their populations and count the number of cities with populations greater than 10 million. But an expert system would be needed to determine the best route from Los Angeles to New York City under specified constraints. From a functional standpoint, decision support systems state facts, whereas expert systems form opinions based on expert knowledge.

Expert systems, of course, also require access to information. In this sense, they are extensions of decision support systems. They contain knowledge as well, which can be in two forms: declarative and procedural. Declarative knowledge is in the form of associations between entities used in the reasoning process and their various properties. Procedural knowledge is in the form of step-by-step methods for determining a given piece of information.

The use of an expert system has many advantages, even for a domain expert (Table 2).

TABLE 1.—*Examples of Medical Expert Systems*

| *Expert System* | *Knowledge Domain* | *Source* |
|---|---|---|
| DXplain | Medical diagnosis | Barnett et al, 1987[1] |
| INTERNIST-1 | Internal medicine | Miller et al, 1982[2] |
| MYCIN | Infectious diseases | Shortliffe, 1976[3] |
| CASNET | Glaucoma diagnosis | Kulikowski and Weiss, 1982[4] |
| ABEL | Acid-base and electrolyte disorders | Patil and Senyk, 1988[5] |
| ONCOCIN | Treatment of cancer | Shortliffe et al, 1984[6] |

TABLE 2.—*Advantages of Using Medical Expert Systems*

- Make available the combined expertise of leading experts in the field
- Factual and procedural knowledge is always available and consistently applied
- All the relevant facts are used in formulating the medication treatment plan
- The steps in the problem-solving process are documented
- Some of the patient record-keeping is automated
- Nonexperts can achieve high levels of problem-solving performance
- The human expert can have more time to devote to difficult clinical problems

## The Development of DETOX

In developing an expert system, a "knowledge engineer" collaborates with a domain expert to elicit the declarative and procedural knowledge that can be represented in a computer program language. In the case of our expert system, we used case histories to elicit the knowledge from the domain expert (D.R.W.). Using a think-aloud technique, the knowledge engineer (R.F.H.) requested that the domain expert actually plan a detoxification process from hypothetical case material. The domain expert described his reasoning verbally while he was working on the problem. The knowledge engineer analyzed notes or tape transcripts of the interview using the methods of protocol analysis to uncover the concepts, facts, conjectures, and relationships used by the domain expert. Once the reasoning for a set of cases was established, the knowledge engineer modeled this reasoning by coding the knowledge employed into the program's knowledge base. The domain expert then reviewed the performance of the system and critiqued its behavior. The knowledge engineer made necessary modifications until the domain expert was satisfied that the system faithfully represented his reasoning. At this point, more cases were considered, and the process began another iteration.

TABLE 3.—*Physician Detoxification Options in the DETOX Program*

| *Drug Class* | *Withdrawal Protocols Available* | *Comments* |
|---|---|---|
| Alcohol | Intermediate- and long-acting benzodiazepines | . . . |
| Beer, wine, liquors | Carbamazepine | |
| | Phenobarbital (available when alcohol is combined with other sedative-hypnotics) | |
| Amphetamine and cocaine | . . . | No specific withdrawal medication is recommended |
| Barbiturates | Phenobarbital | Taper of short-acting benzodiazepines is not recommended |
| Secobarbital (Seconal) | Butabarbital | |
| Pentobarbital (Nembutal) | Taper of barbiturate | |
| Benzodiazepines | Phenobarbital | Withdrawal from long-term, low-dose benzodiazepine use is supported |
| Alprazolam (Xanax) | Carbamazepine | |
| Clonazepam (Klonopin) | Taper of benzodiazepine | |
| Diazepam (Valium) | . . . | |
| Opiates | Clonidine HCl | Clonidine tablets and transdermal patches, alone or in combination |
| Heroin | Methadone HCl | |
| Oxycodone HCl | . . . | |
| Other sedative-hypnotics | Phenobarbital | . . . |
| Meprobamate | . . . | |
| Glutethimide | . . . | |

HCl=hydrochloride

The case material covered both typical and atypical examples. A sufficient number of cases was reviewed to sample the entire domain, including its full range of task difficulty.

The process of writing detoxification schedules is divided into stages: acquiring the patient history, acquiring the drug history, acquiring the physician's medication preferences to be used in the detoxification, generating the detoxification orders, and printing out the results.

The patient's history consists of the standard information, such as age, weight, sex, blood pressure, temperature, allergies, and medical complications, that is obtained from every patient. A physician enters the information into the computer in response to prompts provided by the computer program. The user may recall this information later to make corrections.

The second stage is the acquisition of the patient's drug history. Four data bases are available to assist in this process. One data base references drug information by generic name, a second references trade names, a third cross-references street nomenclature for drugs and the generic names, and a fourth consists of information on alcohol-containing beverages. With these four data bases, the physician identifies the various substances that the patient typically uses.

For each substance identified, the physician is presented with a series of windows requesting information about the amount of drug consumed, the duration of drug use, and the daily time distribution of the total amount consumed.

When the physician is attempting to identify a substance by its street name, a window prompting the user for a purity estimate appears. Additional information on the street value of drugs is provided to assist the physician in converting dollar amounts to milligram amounts.

The third stage of the system is the generation of the detoxification plan. The physician is presented with a list of reasonable withdrawal substitutes based on a patient's drug history. The physician selects from the list, and the expert system produces the detoxification schedule, which is computed from the starting date provided by the physician. The detoxification schedule indicates the daily medication, dosage, and dispensing instructions.

As shown in Table 3, an expert system offers physicians several clinically acceptable withdrawal protocols. There are three such protocols for sedative-hypnotic withdrawal: the phenobarbital substitutions and withdrawal, substituting a sedative other than phenobarbital, and the gradual withdrawal of the drug of abuse. The physician may choose the protocol he or she prefers. The DETOX program also offers carbamazepine substitution for alcohol detoxification. For opiate withdrawal, there are protocols for using clonidine hydrochloride or methadone hydrochloride.

To support its recommendation and allow the physician to review the process, the expert system program also produces a summary of the calculations it did to arrive at its recommendations for detoxification. Finally, a natural language summary of the case is generated that incorporates information from the patient history and the drug history.

Our expert system has been tested by the domain expert. In more than 30 case histories tested, the expert has judged the program's recommendations to be safe and within the range of good medical practice.

The program will next be tested in actual clinical situations to see how physicians can best use the system. The expected benefits of an expert system are access to the combined expertise of leading experts in detoxification, accessibility to the current knowledge about detoxification, a consistent application of all clinically relevant information to a detoxification plan, documentation of the information and calculations used to derive the detoxification plan, and a reduction of paperwork.

## The Future of Expert Systems in Medicine

Expert systems are not commonly used today in medicine, and it will probably be many years before their use becomes standard medical practice.

Before the invention of the computed tomographic scanner, no one would have predicted that computers would become indispensable to the practice of medicine. Now, computerized scanning of patients is routine medicine, and a failure to use such technology when indicated would constitute malpractice in some situations.

Expert systems are a beginning in applying another form of technology to assist physicians in managing the problems of treating substance abuse. Many more applications will no doubt be developed. In time, their use will become routine, perhaps even obligatory, in some types of clinical management problems.

### REFERENCES

1. Barnett GO, Cimino JJ, Hupp JA, et al: DXplain: An evolving diagnostic decision-support system. JAMA 1987; 258:67-74

2. Miller RA, Pople HE Jr, Meyers JD: Internist-I, an experimental computer-based diagnostic consultant for general internal medicine. N Engl J Med 1982; 307:468-476

3. Shortliffe EH: Computer Based Medical Consultations: MYCIN. New York, Elsevier, 1976

4. Kulikowski CA, Weiss SM: Representation of expert knowledge for consultation: The CASNET and EXPERT projects, *In* Szolovits P (Ed): Artificial Intelligence in Medicine. Boulder, Colo, Westview Press, 1982, pp 21-55

5. Patil R, Senyk O: Compiling causal knowledge for diagnostic reasoning, *In* Miller PL (Ed): Selected Topics in Medical Artificial Intelligence. New York, Springer-Verlag, 1988, pp 25-39

6. Shortliffe EH, Scott AC, Bischoff MB, et al: An expert system for oncology protocol management, *In* Buchanan B, Shortliffe EH (Eds): Rule-based Expert Systems. Reading, Mass, Addison-Wesley, 1984

**Addiction Medicine**
**and the Primary Care Physician**

# Methadone Maintenance in the Treatment of Opioid Dependence

## A Current Perspective

JOAN ELLEN ZWEBEN, PhD, *Oakland, California, and* J. THOMAS PAYTE, MD, *San Antonio, Texas*

*We describe the historical underpinnings of negative attitudes towards methadone and how these affect medical decisions. Current developments have increased the understanding of the origins of opioid addiction, such as how receptor system dysfunction may affect the ability to remain abstinent once out of treatment. Specialized topics include the pregnant addict, the role of methadone maintenance in limiting the spread of the acquired immunodeficiency syndrome, and patients with a dual diagnosis. We also describe issues that arise when methadone is used in conjunction with prescribed or abused drugs, noting pharmacologic alternatives and adjuncts to methadone treatment. Finally, we comment on treatment issues such as methadone patients in 12-step programs and the growing legitimacy of this treatment method.*

(Zweben JE, Payte JT: Methadone maintenance in the treatment of opioid dependence—A current perspective, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:588-599)

Current health crises and a growing understanding of opioid addiction are markedly changing attitudes towards methadone maintenance. This method, perhaps the most misunderstood of all drug treatment approaches, has come under new scrutiny because of its key role in the acquired immunodeficiency syndrome (AIDS) epidemic. Although by no means a panacea, it has attracted attention not only because it possibly offers a means to reduce needle use, but also because it provides access to the population of intravenous drug users, allowing a wide variety of educational and prevention-related activities to take place. Medical and counseling staff with no previous exposure are now frequently obliged to deepen their understanding and reassess their attitudes towards this form of treatment. Educational efforts on the part of the American Society of Addiction Medicine are stimulating a revision of opinion based on a better understanding.

Negative attitudes about methadone are pervasive among physicians, patients, and the general public: "It gets in your bones and never comes out." "It's harder to kick than heroin." "It makes you gain weight." "It takes your heart," is the opinion of many addicts on methadone maintenance.[1] Contrary to common impression, many addicts enter methadone treatment highly ambivalently and express an urgent desire to get off as soon as possible. Program staff have the task of helping them shift from the goal of getting off as quickly as possible to that of doing what it takes to make profound life-style changes to support long-term abstinence.

Negative attitudes on the part of physicians and the general public often stem from the perception that methadone treatment is "just substituting one drug for another." This is technically correct; methadone maintenance is drug replacement therapy that substitutes a long-acting orally administered preparation for a short-acting opioid that is self-administered with needles. Even among physicians, the biochemical rationale for this approach is poorly understood and will be elaborated further in this article. It is important to remember that although there is considerable variety in the quality and comprehensiveness of services, many programs provide a wide range of activities intended to foster major life-style changes,[2] and in the long run these efforts are effective.

Methadone maintenance is the most thoroughly studied of all the drug treatment methods. The accumulated research data indicate a reduction in opioid use and criminal behavior and improvements in health status, employment records, and other life-style factors.[3-6] Clinicians should remember these findings, especially when dealing with a patient at an early stage of treatment who is displaying characteristic addictive behaviors. Because methadone maintenance is the "court of last resort," many patients have a long history of problems and do not make behavior changes quickly. Methadone maintenance has the advantage of showing high retention rates compared with other methods,[6,7] and this is a key factor in producing improvement over the long term.

### How Negative Attitudes Affect Medical Decisions

The interaction between a methadone patient and a medical or dental practitioner is often stressful for both participants. Misunderstandings about methadone have resulted in other professionals showing strong, rigid, and harsh attitudes toward patients who take methadone, making it difficult for program staff to foster cooperation with other professionals involved in the patient's care.

In this stressed condition the medical treatment may be affected in one of several ways:

From the 14th Street Clinic and Medical Group, Oakland, California (Dr Zweben), and the Drug Dependence Associates, San Antonio, Texas (Dr Payte). Dr Payte is Chair of the Methadone Treatment Committee, American Society of Addiction Medicine, and a Certified Member of the American Society of Addiction Medicine.

Reprint requests to Joan Ellen Zweben, PhD, 714 Spruce St, Berkeley, CA 94707.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ASAM = American Society of Addiction Medicine
FDA = Food and Drug Administration
HIV = human immunodeficiency virus
NIDA = National Institute on Drug Abuse

• *Treatment is denied.* Sometimes when a physician is informed that a patient suffers from opioid dependence and is being treated with methadone, the physician simply refuses to treat that patient.

• *Treatment is diminished.* The physician's response to the patient's expression of subjective concerns may be altered, based on the distrust and disgust resulting from negative attitudes. The physician may withhold needed symptomatic medication, thus causing unnecessary discomfort and pain (see section dealing with the methadone-maintained patient in medical or dental settings).

• *Treatment is discouraged.* In cases where treatment is offered in a begrudging manner, the patient may decide that the needed treatment is not worth the ensuing pain, hopelessness, and helplessness. A healthy therapeutic relationship cannot develop when the patient sees health care providers as adversaries. The patient may prefer to do without treatment rather than tolerate the situation and may drop out of treatment or leave a hospital against medical advice. This perpetuates the stereotype that all patients on methadone maintenance are uncooperative.

• *Treatment is conditional.* A patient may be treated only if he or she will submit to an attempt at withdrawing from methadone maintenance. The outcome of the inappropriate withdrawal process is usually a total disruption of treatment of the condition leading to the consultation or hospital admission and the treatment of the addictive disorder as well. As the abstinence syndrome develops, the patient becomes agitated and will often act out in an effort to impress staff with the need for relief. This behavior is seen as that of an ungrateful and unmanageable patient being disruptive.

Clearly the above situations do not lend themselves to the delivery of quality health care. To deny quality health care because a person is suffering from a specific disorder (opioid dependence) and is engaged in a specific treatment (methadone maintenance) is inappropriate and counterproductive. Some of these problems grow out of unfamiliarity with the recovery process and what constitutes reasonable expectations of the patient at each stage. Another source of difficulty is the lack of ability and skill in handling manipulative behavior. A physician who has an underlying image of the good patient as compliant may become frustrated and embittered at some of the behavior characteristics of the patient who is in early treatment. In settings where the staff is straightforward in dealing with typical behavior patterns, tensions are much reduced.

When a patient on methadone maintenance seeks medical or dental care, communication between the providers is important. The letter in Figure 1 can serve as an introduction to methadone maintenance in settings where staff have little experience with it. Through a better understanding of the situation, the new service would find that the methadone maintenance program and its staff can be of valuable help in the care of a mutual patient.

Pilot programs are now under way that would return rehabilitated patients on methadone maintenance to general primary medical care. A patient who has become stable and free of the psychosocial aspects of the disease but in whom continued medication therapy (methadone maintenance) is indicated would be referred to a primary care physician for "medical maintenance." The rehabilitated patient would then be an ordinary patient in routine care, just like those taking medications for hypertension, arthritis, and diabetes mellitus.

## The Origins of Opioid Addiction

It is commonly agreed that addictive disorders are complex phenomena involving the interaction of biologic, psychosocial, and cultural variables, all of which need to be addressed for treatment to be effective. Medical intervention is one part of the treatment and needs to be seen in the context of the whole. The recovery tasks are basically similar no matter what a patient's drug of choice[8,9]; however, an understanding of the specifics of opioid dependence is crucial to forming appropriate expectations of patients. Much of the destructive behavior of treatment professionals towards methadone-maintained patients results from these inappropriate expectations, especially the view that heroin addicts would stay off opiates (without methadone) if they were only motivated enough.

Vincent Dole, who, with his wife Marie Nyswander, pioneered the use of methadone, has always held the view that there was something unique about opioid addiction that made it difficult for patients to remain drug free. In their early work Dole and Nyswander proposed that opioid addiction involved a "metabolic disease,"[10,11] and it is this theme which continues to be explored and elaborated. In 1988 Dole won the Albert Lasker Clinical Medicine Research Award for his work in this area and summarized his views in a paper in *The Journal of the American Medical Association:*

> It is postulated that the high rate of relapse of addicts after detoxification from heroin use is due to persistent derangement of the endogenous ligand-narcotic receptor system and that methadone in an adequate daily dose compensates for this defect. Some patients with long histories of heroin use and subsequent rehabilitation on a maintenance program do well when the treatment is terminated. The majority, unfortunately, experience a return of symptoms after maintenance is stopped. The treatment therefore, is corrective but not curative for severely addicted persons. A major challenge for future research is to identify the specific defect in receptor function and to repair it. Meanwhile, methadone maintenance provides a safe and effective way to normalize the function of otherwise intractable narcotic addicts.[12(p3025)]

Dole thinks that the persistent receptor disorder results from chronic opiate use, leading to down-regulation of the modulating system and possibly also to a suppression of endogenous ligands. Two key questions for future research are whether some preexisting condition enhances the vulnerability of some patients more than others and whether long-term addicts can ever recover normal functioning without maintenance therapy.

Dole notes that newly available techniques for sensitive analysis, including specific ligands for analysis of receptor binding, permit renewed investigation:

> What is needed now are methods to assess the kind and degree of receptor derangement in addicts and a better understanding of the function of this modulating system in response to physiological stress. With a more detailed understanding of addiction in molecular terms, a fundamental cure may be possible.[12(3027)]

*Heroin Versus Methadone*

The crucial properties that distinguish methadone are that it is a long-acting opioid that can be orally ingested, instead of a short-acting drug administered with needles. Dole notes that the essential difference between heroin use and methadone is

> the stability of receptor occupation, which permits interacting systems to function normally. The physiological and behavioral disturbances in heroin addiction apparently are consequences of the rapid changes in status of the endogenous narcotic receptor-ligand system. When the addict takes short-acting narcotics, the system cycles between abstinence and narcosis several times a day. A stable state of adaptation is impossible.[12(p3026)]

## Pharmacologic Features of Methadone

Methadone hydrochloride is a synthetic opioid-agonist drug that acts primarily at the $\mu$-opioid receptor sites.[13] As an analgesic, it is equal in potency and duration to morphine.[14(p518)] Significant differences exist between the initial effects of use in an opioid-naive person and in the effects of long-term use in a tolerant person. It also acts differently according to whether it is used intravenously or orally. When taken intravenously, the portal circulation is avoided and, being highly lipophilic, it readily crosses the blood-brain barrier, producing a rapid onset of the sought-after "rush."

Taken orally, it behaves in a much different manner. Its

### Letter to Physicians and Dentists Treating Patients on Methadone Maintenance

The bearer of this letter is a patient in a methadone maintenance treatment program. Methadone-maintained patients occasionally need treatment for medical, psychiatric, surgical, and dental conditions. Health professionals are not always familiar with addictive disease and the various forms of treatment, including methadone. In some cases the reaction to methadone-maintained patients is based on fear, anger, prejudice, disgust, or other negative subjective responses, none of which contribute to providing quality health care. Many patients are reluctant to provide information to health professionals about their addiction and treamtent with methadone because of previous bad experiences. The purpose of this letter is to describe the most common problems encountered and to offer any assistance we might be able to provide.

Addiction is now widely accepted to be a disease or a group of diseases. Addictive disease can be characterized as a chronic, progressive, probably incurable, and often fatal disorder. The principal diagnostic features are obsession, compulsion, and continued use despite adverse consequences (loss of control). Our program provides counseling services to help the patient make the life-style changes needed to address the many dimensions of this disorder.

Methadone has been used in the treatment of opioid dependence for about 25 years. Its long-term administration has been found to be both effective and safe. Methadone-maintained patients develop nearly complete tolerance to the analgesic, sedative, and euphorigenic effects of methadone at an established maintenance dose. Tolerance does not develop to the effect of preventing the onset of the abstinence syndrome. Methadone has a half-life in excess of 24 hours. It has a relatively flat blood plasma level curve that will prevent the onset of the abstinence syndrome for more than 24 hours without causing any sedation, euphoria, or impairment of function.

The management of pain in a methadone-maintained patient is the most common problem we encounter. Because the patient is fully tolerant to the maintenance dose of methadone, *no* analgesia is realized from the regular daily dose of methadone. Relief of pain depends on maintaining the established tolerance threshold with methadone and then providing additional analgesia. Nonnarcotic analgesics should be used when pain is not severe. In the event of more severe pain, the use of opioid-agonist drugs is appropriate. The dose of an opioid-agonist drug may need to be increased because of the cross-tolerance to methadone. Also, the duration of analgesia may be less than usual. Opioid-agonist/antagonist drugs such as pentazocine (Talwin), butorphanol tartrate (Stadol), and nalbuphine hydrochloride (Nubain) should never be used in a methadone-tolerant person. Severe opiate abstinence syndrome can be precipitated by drugs of this type.

The administration of opioid-agonist drugs should be closely supervised in terms of quantities and duration. Prescribing for self-administration by the patient should be avoided. If it is absolutely necessary to prescribe for self-administration, the amount should be for no more than 24 hours and refills carefully controlled. Similar precautions are indicated in the prescribing of sedative-hypnotic and central nervous system-stimulating drugs. The abuse potential of *all* benzodiazepines is high.

At times admitting physicians are tempted to treat the opioid dependence itself. This is usually attempted by doing a graded reduction of methadone dose. If successful, the graded reduction may result in a reduction or elimination of the physiologic dependence, but it has no effect on the disease itself. Even after the methadone treatment is discontinued, significant signs and symptoms of abstinence may persist for several weeks. The relapse rate associated with detoxification alone approaches 100%. A relapse to street or illicit drugs increases the risk of overdose, hepatitis, AIDS, and a host of other biomedical, psychosocial, and legal complications.

Under some circumstances an intervention can be accomplished during a hospital stay for other conditions. Such a process should involve experienced professionals with a strong emphasis on continuity of care on discharge.

If you have any questions or concerns about our mutual patient in relation to methadone or drug dependence, please call us. We would be delighted to hear from you.

Sincerely,

**Figure 1.**—This introductory letter could be taken by a methadone-maintained patient to a dentist or physician providing the patient additional health care. AIDS = acquired immunodeficiency syndrome

absorption from the gastrointestinal tract is essentially complete. There is extensive initial hepatic uptake—around 90%. Methadone is then gradually released from hepatic binding (storage) sites in an unchanged form into the effluent blood. The liver probably plays a major role in the large reservoir of methadone postulated by Dole and Kreek in 1973.[15] They suggested that this reservoir of methadone, nonspecifically bound in tissues and in equilibrium with methadone in plasma, would be necessary to explain the relatively low peak plasma levels and the relatively high steady-state levels 24 hours after a dose.[13]

The result is a flat curve of methadone blood plasma levels over a 24-hour period, with peak levels (2 to 6 hours) normally less than two times the nadir or trough level (24 hours). This accounts for the constant availability at the appropriate opiate receptor sites.

> Constant availability of drugs to specific receptors is essential for steady-state maintenance of the tolerant and dependent state, and it is this constant availability of the drug to specific receptors, resulting in a steady state, which has been essential for the pharmacological, physiological and thus clinical efficacy of methadone maintenance treatment.[13(p55)]

This phenomenon is essential to the normalization of endocrine and neuroendocrine functions that occurs with the long-term administration of methadone. In contrast, the "on-off" effect of short-acting opiates such as heroin prevents tolerance and adaptation to all but the most acute effects. Fortunately, tolerance to the narcotic-withdrawal prevention effect, and tolerance to the reduced craving, a key property of methadone, does not develop, even after 20 years of maintenance.[13]

One widely held fallacy is that "methadone keeps you high 24 hours a day." In fact, the "rush" or high is a result of changing blood levels, whereas methadone is long acting (24 to 36 hours), allowing a patient to receive a dose and function in a stable manner. Kreek says,

> [I]f the proper dose of methadone is administered . . . then no euphoria and no narcotic effect of any kind can be perceived by the patient, or observed or measured by the physician or scientist . . . and withdrawal symptoms will not appear for 24 hours or more.[13(p56)]

Physicians have a wide therapeutic window in which to adjust the dose between the points of craving and somnolence. Dose adjustment may take some weeks, but a patient on methadone maintenance should not be "nodding out" (sedated). The patient may feel some sedation immediately after a dose increase, but tolerance occurs within a few days. Stability of functioning can be achieved with methadone, making it possible for the patient to participate normally in job and familial activities.

It is noteworthy that nonmedical influences may play a significant role in dosing practices. The goal of physicians is to achieve a therapeutically effective dose. The optimal dose is one that keeps the blood levels in the range of 150 to 600 ng per ml.[12] In some settings, however, local politics dictate dosing practices; maximum doses may be decided by policy—such as state or county regulations—rather than by medical criteria. The tacit assumption is that methadone is at best a necessary evil; hence, patients should be given the least possible amount. For example, some states or clinics place a ceiling of 40 mg per day, even though clinical experience and literature reviews indicate that this may be inadequate to maintain the necessary plasma concentrations to be effective.[16-18] When a distressed patient then supplements his or her methadone with illicit heroin, the ineffectiveness of methadone is confirmed in the minds of the regulators. Whenever possible, physicians need to take an educator's role to influence the promulgation of sound regulations and policies. Clinically, the proper dose of methadone prevents the onset of withdrawal symptoms, reduces craving, and exerts an apparent "blockade" on the effects of heroin.

There appears to be considerable variation in the rate at which patients metabolize methadone—due to differences in metabolism and absorption from the gastrointestinal tract—and hence in what may be the appropriate dose. Tennant studied a group of 18 heroin addicts who were maintained at 80 mg per day and were still abusing alcohol and other drugs.[19] When their doses were raised to 100 mg per day, improvement was noted in levels of signs and symptoms and in a modest increase in the 24-hour blood plasma levels of methadone. The majority remained below accepted therapeutic levels, suggesting that doses in excess of 100 mg per day might be considered for this subgroup of patients. One subject who experienced an increase to above 200 ng per ml said that his dose was "holding," and there was no further drug and alcohol abuse. Tennant suggested there is a subgroup of patients with aberrant metabolism who achieve better social stability and reduced illicit drug use at doses above 80 mg daily.

## Getting Off Methadone Therapy

The difficulties in getting patients off methadone maintenance, and their lack of success in remaining abstinent, have been the source of much misunderstanding and controversial policies. McLellan reviewed a group of studies and concluded that only 10% to 20% of patients are able to maintain abstinence,[20] a range consistent with the impression of clinicians and findings of subsequent studies. More optimistic estimates set the abstinence rate around 30%.[21] There is no question that the magnitude of the life-style changes required is a major determining factor. Giving up a heroin habit requires addressing personality patterns, family life-styles, job skills, friendship patterns, and recreational involvements, to name only some obvious variables. Methadone itself is only a tool to free the patient to undertake these other tasks.

A series of studies conducted at the University of California, San Francisco, explored the difficulties in going from maintenance to abstinence.[22-24] When the researchers initially set up the Tapering Network Project, they were struck by how frightened prospective patients were to even attempt to taper off, even when offered a wide range of supportive services, because of their fear of jeopardizing their hard-won stability. This observation was supported by a study done elsewhere that described an intense fear of detoxification in almost a third of a group on methadone maintenance.[25] As the studies progressed, staff and patients alike noted many barriers to getting off methadone maintenance. These included a fear of relapse because of the easy access to drugs in the environment, worries about motivation or about "being strong enough," physical discomforts, and withdrawal difficulties.[22] Patients tapering off described problems with social isolation; the identity transition to "former heroin addict" and the loss of friends, including intimates, that took place; and a "postmethadone syndrome" that was characterized by vulnerability, dramatic mood swings, and disordered thinking for a period of six months following the withdrawal from methadone.[24] Important determinants of success were whether a patient had been in treatment a long time, was

employed, was assimilated into the nondrug world, was motivated to give up methadone, and had the confidence of staff members that he or she would do well. Those patients with the highest degree of rehabilitation seem to have been the most successful in tapering off methadone therapy.[23]

Many clinicians on the front lines of treating addiction are deeply impressed by the sincerity and struggle of these patients attempting to taper off drugs and remain abstinent and are convinced that motivational factors are not the key variable. Biochemical factors may play an important role in understanding why so few patients successfully detoxify and remain abstinent. Kreek comments on the significance of the role of the endogenous opioids in addiction, offering three different hypotheses that have been proposed:

> (1) narcotic addiction could be a disease of endorphin deficiency; (2) a disease of endorphin excess with failure to respond to endorphins; or (3) a disease in which there may be an altered feedback control of synthesis, release or degradation of one or more of the classes of endogenous opiates, or altered receptor response. The latter [sic] seems most likely.[13(p59)]

Kreek has participated in ongoing studies of drug-free former heroin addicts and drug-free former methadone-maintained patients and comments that early studies support the view that several neuroendocrine responses are abnormal for a long time after abstinence is achieved. She speculates that these abnormalities contribute to the behavior of drug seeking. In their original work Dole and Nyswander hypothesized that there were physiologic factors preventing heroin addicts from functioning normally, thereby necessitating replacement for an indefinite period.[11] Dole continues to hold this view in his current work,[12] stating that receptor system dysfunction played a key role in why such a high proportion of methadone-maintained patients relapsed once they tapered off methadone. If indeed a patient's brain chemistry remains abnormal for a protracted period of time, it is important to develop ways to normalize it if there is any hope of getting large numbers of patients off methadone maintenance. Additional complexities are presented by patients with a dual diagnosis who may be using heroin or methadone to medicate a psychiatric disorder. In such cases, it is important to inquire about what occurred in previous attempts at detoxification to assess the likelihood that a psychosis or depression may emerge as the methadone taper progresses.

Currently many considerations require a reassessment of the pressure to get patients off methadone maintenance. Historically, arbitrary time limits for being on methadone have often been selected without reference to previous research. These were often embodied in federal and state regulations and state-funded health insurance and created pressure for detoxification and termination of treatment independent of clinical considerations. Although the regulations themselves often allowed flexibility, their interpretation by those who enforced them was frequently more rigid and uncompromising. One study of the effects of such time limits indicated that most of the affected maintenance patients fell far short on almost every variable accounting for successful detoxification.[26]

The effectiveness of methadone maintenance should not be judged by what happens once a patient terminates. Newman likened the validity of this approach to gauging the effectiveness of birth control pills by counting the number of pregnancies that occur after the administration is discontinued.[27] It is important to challenge the tendency to judge treatment effectiveness mainly by looking at a patient after detoxification from methadone, rather than focusing on whether or not the person is living a socially productive life free of illegal drug use. As Lowinson has pointed out, rehabilitation, not abstinence, is the primary goal of methadone maintenance treatment.[28] The standards for those remaining on methadone maintenance are high. Guidelines set by the National Institute on Drug Abuse (NIDA) judge efficacy by the ability to get drug abusers to discontinue drug use, decrease criminal behavior, and increase the likelihood of being employed.[29] Newman pointed out that the criteria for success

> reflect social, as opposed to clinical, objectives, which are unthinkable in other fields of medicine . . . [M]ethadone maintenance is dismissed by many and damned by others because it does not "cure" patients or render them immune from such societal ills as unemployment, alcoholism, marijuana smoking, and criminality. In other words, methadone maintenance has come to be evaluated by virtually every criterion except a decline in heroin use.[27(p448)]

Abstinence models, exemplified by therapeutic communities or the 12-step philosophy, inspire more enthusiasm than methadone maintenance, but neither patients nor the community is well served by continual attempts to force them to meet inappropriate and inflexible standards. Patients wishing to taper off methadone should be given every possible type of support. A variety of these activities have been described in the work of the Tapering Network Project.[22,24] Patients should not be treated as second-class citizens if they choose to continue methadone treatment or if they are unable to go off or stay off methadone maintenance without jeopardizing their hard-won gains.

## Pregnancy, Opioid Dependence, and Methadone Treatment

Pregnant opioid addicts present a sensitive challenge to clinicians. The scientific literature on the subject is voluminous though uneven and at times contradictory. Fortunately there is a general consensus that provides guidelines for caring for pregnant opioid addicts in a safe manner.

Two types of pregnant opiate addicts are seen in methadone treatment programs. One is the street addict who seeks treatment after becoming pregnant, at times late in the pregnancy. The other is a patient on methadone maintenance who becomes pregnant.

The first type calls for a choice between methadone maintenance and withdrawal. Since the early 1970s, methadone maintenance has been the preferred choice.[30] Fetal distress was found to be associated with withdrawal,[31] as are first-trimester miscarriages and premature labor. Even in cases where detoxification is achieved, there is the predictable frequent return to the use of heroin or other drugs (S. Schnoll, MD, PhD, oral communication, 1989).

Stimmel and colleagues did a study from which they concluded that supervised methadone maintenance is compatible with an uneventful pregnancy and delivery.[32] Methadone maintenance early in pregnancy is associated with longer gestation and increased birth weights compared with the outcome in untreated addicts.[33] When compared with drug-free controls, in utero exposure to methadone is associated with lower birth weights and smaller head circumferences, but by 6 months of age the children do not exhibit any general developmental sequelae.[34(p276)] Still, methadone-maintained mothers need high-risk prenatal care.

Of utmost importance is that a patient's methadone dose

(at any time, but especially during pregnancy) be individually and clinically determined by a physician who is knowledgeable and experienced in addiction medicine, with an emphasis on methadone treatment. An arbitrarily low dose, determined by policy rather than clinical judgment, almost always results in increased opiate use, polydrug abuse, and decreased program retention and compliance. Being in a methadone program may provide the leverage for a patient to get into a needed support system, such as prenatal care, parenting classes, and the usual counseling, therapeutic, and other supportive services offered by the program. Clinicians must be aware that because of altered methadone pharmacokinetics associated with pregnancy,[35] particularly in the third trimester, the methadone dosage might need to be increased to produce the steady-state condition needed to be effective. Efforts to maintain a low dose during pregnancy are often based on an assumption that a higher dose will result in a more severe manifestation of the neonatal abstinence syndrome. The literature does not support that assumption; for example, studies could not find a relationship between the methadone dose during pregnancy and the presence of withdrawal symptoms in babies.[32] Sometimes splitting a patient's dose, giving half in the morning and half late in the day, will facilitate steady-state maintenance. In all cases, doses should be adjusted according to what is required for stability and comfort.

Patients addicted to more than one drug in whom opiates play a substantial role pose a much greater challenge. Such patients may well be appropriate for methadone maintenance. It is not uncommon for patients maintained on an adequate dose of methadone to discontinue the casual or episodic use of other substances. When continued use of nonopioid drugs is characterized by strong compulsion (loss of control), or physiologic dependence, or both, patients would be best withdrawn in a setting that affords careful fetal monitoring and a drug-free environment. Methadone maintenance can be continued or initiated at the same time.

Contrary to the impression given by television and other media coverage of the newborn abstinence syndrome, the withdrawal associated with maternal methadone maintenance is fairly straightforward and uncomplicated.[10] It is a popular myth that methadone withdrawal is more severe than any other. In reality, because of the long plasma half-life, the abstinence syndrome develops slowly, is of moderate intensity, and lasts a long time. Heroin or morphine addiction, on the other hand, results in a rapid onset of a more intense withdrawal that is fairly brief in duration. Protocols are available that provide for scoring the severity of the neonatal abstinence syndrome and scheduling the appropriate medication to accomplish withdrawal in a comfortable and safe fashion.[36]

## The Role of Methadone Maintenance in Limiting the Spread of AIDS

The urgent need to reduce the prevalence of intravenous drug use has brought new problems and new resources to programs. Although methadone maintenance is not a panacea, it has much to offer in limiting the spread of AIDS.[37,38] Clinics provide accessibility to large numbers of intravenous drug users, making them an excellent site for prevention and education programs. Patients coming for methadone detoxification can be offered screening, education, and limited counseling. Those participating in methadone maintenance also have a continuing forum to discuss their concerns and resistances to practicing safe sex and sound needle-cleaning practices if they are still using drugs. Finally, the overall treatment effort yields incremental gains, as an abstinent addict is in a position to exercise better judgment than an intoxicated one.

A recent (1988) NIDA report summarizes data that the longer a patient has been in methadone treatment, the lower the rate of seropositivity for the human immunodeficiency syndrome (HIV).[39] This review presents data from New York, Sweden, and Italy. Bourne, reporting on rates of HIV seropositivity among four groups of drug addicts in Bergamo, Italy,[40] found that patients on methadone maintenance had lower rates than patients in therapeutic communities, legal custody, or those who were admitted to hospital for other reasons. In a three-year study of patients in large Eastern US cities, Ball and co-workers found methadone maintenance to be effective in reducing intravenous drug use and needle-sharing practices.[41]

Concerns have been raised about the effects of methadone on the immune system, as laboratory studies have shown immunosuppressant effects of certain opiates.[42] It appears, however, that patients on methadone maintenance show better immune system functioning than street addicts.[43,44] Batki proposes that methadone maintenance has overall beneficial effects by reducing intravenous drug use and its insults to the immune system and by other life-style changes, and that these outweigh any possible suppression of immunity by the direct chemical effects of methadone.[38] This is consistent with the findings of Novick and associates that methadone-maintained patients in treatment for five or more years have significantly lower seropositivity rates.[45] Later work by Novick and colleagues supports the view that previously existing abnormalities of cellular immunity can be normalized by successful long-term methadone treatment.[46]

Great efforts are being made to integrate AIDS-related activities as fully as possible within methadone maintenance programs. Enrichment activities include both medical services and counseling focused on grief and related emotional losses, stress reduction, and health maintenance. The Program for AIDS Counseling and Education (PACE) offered as part of the methadone maintenance unit at San Francisco General Hospital Substance Abuse Services provides one example.[38,47] Recently this group, reporting a 12-month follow-up on patients in their program,[47] concluded that seropositive addicts in their program reduced their drug use early in maintenance treatment but made less dramatic changes in their sexual behaviors.

## Obstacles to the Expansion of Methadone Treatment

Efforts to expand the capacity of methadone maintenance treatment in response to the AIDS epidemic have met with many obstacles owing to federal and state regulations formulated in response to concerns from an earlier era. In addition to being the most thoroughly studied, methadone treatment is the most regulated of any form of medical treatment.

The first step occurred about 20 years ago in response to the flagrant prescribing of methadone tablets by a fairly small number of physicians. The Food and Drug Administration (FDA) took action, drastically restricting the availability of methadone. Methadone was removed from retail pharmacies and was made available only to hospital-based pharmacies,

which faced further restrictions as to how prescriptions could be filled.

At the same time, the access to methadone for treatment of opioid dependence was restricted to holders of an "IND" (investigational new drug) exemption. Methadone has since been approved for the treatment of opioid dependence.

By the mid-1970s the FDA had established detailed regulations, guidelines, and standards of care. The early regulations left little room for clinical judgment, covering such items as initial and maximum doses of methadone, frequency of attendance at a clinic, urinalyses, take-out medications, staffing patterns, record-keeping components, reporting requirements, and conditions under which a patient could be admitted to treatment. The regulations also called for the creation of a "state methadone authority" that was to establish or adopt existing regulations and guidelines and take part in the process of licensing and evaluating programs.

Federal agents began making surprise inspections of programs to ensure compliance. Actions for noncompliance could consist of a letter stating the deficiencies and requesting assurance that the items would be corrected, to closing a program down, complete with legal charges. Programs quickly learned that survival depended on the condition of the records and not the patients.

There has been considerable speculation as to the motivation or purpose for the regulations that represented an unprecedented intrusion into the practice of medicine. Some think there was a sincere intention to ensure quality care, others that the process was one of political compromise, and still others that the intention was to discourage the growth of this unpopular form of treatment. Evidently some provisions were made in the absence or disregard of scientific clinical investigations and experience.

It is beyond the scope of this article to discuss the various state regulations. Some states perceived a need to take a much tougher stance than the FDA. In any given situation, the more stringent regulation will apply. Practicing physicians need to be thoroughly familiar with both state and federal regulations. For several years the trend at the federal level has been to reduce the complexity and detail in favor of relying more on clinical judgment. The states have been slow to follow this excellent example.

It should be noted that existing regulations deal in large part with patient record-keeping requirements. Issues such as decreasing the use of illicit drugs, reducing the incidence of criminal activity, increasing employment, and improving social function are ignored in favor of requiring a properly executed, dated, signed, and countersigned treatment plan.

The FDA and the NIDA are proposing revisions in existing regulation that would provide for minimum-service, interim methadone treatment in an effort to combat the spread of AIDS by getting more people off intravenous heroin use until such time as patients can be admitted to a comprehensive treatment program. Many prefer that the necessary resources be committed to the rapid expansion of quality comprehensive methadone treatment programs.

The FDA and the NIDA are also proposing pilot programs to lead to the development of performance-based standards for monitoring programs to replace the current system. Change at the federal level will have little positive impact unless the various states become involved in making similar constructive revisions.

## Patients With a Dual Diagnosis

The relationship between addiction and other psychological disorders is highly complex. For many decades, addiction was viewed by professionals as a manifestation of psychological problems. It was then assumed that if these "underlying" issues were addressed, the addiction problem would take care of itself. When this did not occur, addicted or alcoholic persons were often dismissed as "untreatable" by professionals. Many sought help from the professional community and did not find it, resulting in the growth of a sizable portion of the recovering community that remains distrustful, alienated, and bitter towards professionals. Subsequent models that emerged in the addiction field addressed the needs of people in recovery but tended to be overly optimistic about the degree to which most of a recovering person's major life problems would be ameliorated by sobriety and consistent participation in a 12-step program.[48] This, too, did a disservice to persons in recovery who had other problems that needed to be addressed. Current perspective emphasizes understanding and responding more adequately to the needs of these patients.[49-52]

For a variety of reasons, methadone maintenance attracts people with a full spectrum of disorders. Certain characteristics of this therapy lend themselves to meeting the needs of moderately or severely disturbed patients. Federal and state requirements mandate a frequency of attendance not generally found in other forms of outpatient treatment. In the United States, even patients in the best of standing must come to the clinic weekly; no more than six days of take-home medication can ever be given. Disturbed patients are frequently unable to meet the behavioral criteria necessary to qualify for taking medication home and hence come to clinic more frequently. This level of structure and contact in itself appears to be a major stabilizing factor. The relatively brief interaction with a friendly dispensing nurse and other staff provides comfort and reassurance to patients and offers the opportunity for regular observation by staff. Other treatment methods, such as therapeutic communities or conventional outpatient programs, may require more capacity for insight and confrontation than a patient can tolerate. Hence, methadone maintenance programs tend to have a group of these patients who would be unable to meet the requirements elsewhere.

Methadone itself has variable effects on these patients, who may express a preference for it over antipsychotic medication. Many counselors have noted that there is a subgroup of patients, like one who referred to methadone as his "sanity syrup," who appear to be calmed and stabilized by taking it; when their doses drop, they become disorganized. Berken and colleagues have described one such schizophrenic patient whose rages were greatly diminished by the use of methadone.[52]

The antipsychotic properties of opioids are intriguing and not well understood.[53,54] Brizer and associates reported a notable improvement in a small sample of chronically and severely ill patients given methadone as an adjunct to neuroleptic therapy.[53] Even the patients' thought disorders were reduced. The authors suggested several possible explanations, including a specific antipsychotic effect of methadone, an anxiolytic effect, or a synergism between neuroleptics and methadone.

Methadone is but a tool to make other kinds of changes possible. Most methadone maintenance programs are

equipped to provide case management and counseling that is fairly limited in scope. Psychotherapy has a legitimate role for methadone-maintained patients suffering from moderate to high levels of psychological disorder[55,56] and with certain psychiatric diagnoses, particularly depression. When possible, nonpharmacologic interventions should be employed, but when medication is indicated it should be used. Careful monitoring is necessary, especially because of the tendency of these patients to use alcohol and other drugs, at least episodically.

## Methadone and Other Drug Use

### *Alcohol*

In recent years there has been much discussion about alcoholism, cocaine use, and other drug use or abuse that occurs in methadone-maintained patients. Such observations at times appear to be an indictment of methadone maintenance as a method of treatment. Methadone, as a pharmacologic agent in the treatment of addictive disease, is opioid-specific. All that can be expected of methadone treatment by itself is at best to eliminate all use of illicit opioids and, at worst, to reduce such use. This is accomplished by preventing the onset of the opioid abstinence syndrome and reducing the effects of opioid drug hunger. Contrary to popular opinion, an increased use of alcohol and other drugs is not caused by addicts' participation in methadone treatment.

Alcohol use among methadone patients has been a major concern since the early days of methadone maintenance. Stimmel, in reviewing the literature, concludes there is no evidence to support the idea that the use of methadone produces problem drinking ("Methadone Maintenance and Alcohol Use," *Grassroots* 1981, pp 13-30). He also examines the evidence concerning the consumption of alcohol among populations socioeconomically comparable with heroin-dependent persons and concludes that alcohol consumption or the prevalence of alcoholism is no greater in this population than in a matched group of persons not dependent on methadone. More recently Anglin and co-workers again evaluated the hypothesis that methadone maintenance can be causally implicated in an increased consumption of alcohol.[57] They have reported evidence for an inverse relationship between alcohol and heroin consumption throughout addicted persons' lives, and they suggest that the use of alcohol during methadone treatments follows an established pattern of increased alcohol use following a reduction in heroin intake.

Treatment of a methadone-maintained patient with alcoholism can be approached in the same manner as for other patients not on methadone maintenance. Inpatient or outpatient detoxification and treatment can and should be accomplished while methadone maintenance is continued.[58] Where (as is often the case) a lack of motivation is a problem, a combined behavioral-pharmacologic treatment in which methadone treatment is made contingent on taking disulfiram has been shown to decrease alcohol consumption and the incidence of arrests while increasing employment.[59]

Questions invariably arise in the case of a methadone-maintained patient being treated for severe liver disease. Novick and associates concluded that methadone maintenance was not associated with the development of cirrhosis.[60] Methadone-maintained patients who abuse alcohol and in whom cirrhosis develops should be continued in methadone maintenance while appropriate treatment of the alcoholism is given. An earlier study examined the disposition of methadone in maintenance patients with severe liver disease.[45] In the patients with liver disease the apparent methadone half-life was longer but there was no increase in peak plasma levels; in fact, they were lower. Novick and colleagues in that study hypothesized that the reduction of methadone metabolizing by the liver was offset by damage to the liver's capacity to store and release unchanged methadone. Methadone maintenance may be continued in stable patients with severe alcoholic liver disease, but it requires careful supervision.

### *Cocaine*

As noted previously, patients on methadone maintenance are not immune to other diseases or abuse of nonnarcotic drugs. Those living in areas with a high incidence of cocaine use show evidence of joining in this activity. Again, methadone treatment has been singled out for its failure to prevent or cure cocaine abuse. Patients being maintained on methadone therapy are frequently observed and subject to random urine drug screens; hence, cocaine use is quickly detected in such patients. Cocaine use results in wide-ranging functional deterioration that is rapid and dramatic.[61] Hanbury and co-workers showed that some of their subjects stopped using cocaine as a result of entering methadone maintenance.[62] Many clinicians are observing previously stable methadone-maintained patients deteriorate as a result of cocaine use but think that continuing participation in the methadone program provides access and some leverage in dealing with the problem, which terminating the treatment does not.

There is a direct relationship between the escalating use of cocaine and an increasing amount of crime and violence. This relationship has been attributed to the effects of the drug itself and the costs and the pattern of use. Despite the wide availability of "crack" (smokable) cocaine, many methadone-maintained patients prefer to continue their long-term romance with the needle by using cocaine intravenously.

Cocaine use, like that of amphetamines, can result in a dramatic and reversible paranoid state. The content of the paranoid delusions may lead to violence. Inpatient treatment is usually required to deal with the intense craving associated with cocaine addiction. Those who use cocaine by nasal insufflation are more likely to respond to outpatient treatment.

### *Prescribed Medications—Some Problematic Interactions*

Benzodiazepines are popular among methadone-maintained patients. They are obtained both by prescription and through diversion to street sales. While there is no pharmacologic interaction between methadone and diazepam, there is an additive effect. Stitzer and colleagues studied diazepam use among patients on methadone maintenance.[63] They found that the majority reported taking diazepam in a single daily dose within an hour of ingesting their methadone. Also, patients using heroin on the street may come in addicted to diazepam they used to relieve opiate withdrawal symptoms.

Many in the field of addiction medicine consider the use of benzodiazepines contraindicated in patients with addictive disorders.[64] The use of this class of drugs is often counterproductive in terms of recovery and should be limited to clear psychiatric indications where other measures are not adequate and with close supervision.

*Phenytoin.* The abstinence syndrome may result from the use of therapeutic doses of phenytoin in methadone-main-

tained patients. It is likely that phenytoin accelerates methadone metabolism. Methadone dose adjustments are likely to be necessary if phenytoin therapy is either initiated or discontinued. Valproic acid, unlike other anticonvulsants, does not appear to affect methadone metabolism.[65]

*Rifampin.* Rifampin is a potent inducer of the hepatic microsomal system. It is known to cause clinically significant interactions when combined with many drugs, including methadone.[66]

*Desipramine hydrochloride.* Preliminary studies suggest that desipramine hydrochloride may be effective in the treatment of cocaine dependence. Methadone is known to slow the degradation of desipramine so that lower doses may prove effective.[67]

*Phenobarbital.* The literature is not definite regarding the effects of taking phenobarbital and methadone, but there are scattered anecdotal and case reports.[68] One of us (J.T.P.) has observed withdrawal induced by attempting to substitute phenobarbital for benzodiazepine detoxification in a methadone-maintained patient. Methadone patients may be withdrawn from benzodiazepine use by administering another benzodiazepine in a graded dose reduction.

*Anesthesia.* Methadone-maintained patients tolerate all types of anesthesia. It is important that an anesthesiologist be fully informed of the drug history and especially current medications. An increased tolerance to some agents may occur. The use of opioid agonists or antagonists must be avoided.

*Pain management.* The treatment of pain in a patient on methadone maintenance is really quite simple but does seem to account for the greatest single source of error in patient management. A failure to deal effectively with pain in patients being maintained on methadone is a common cause of disruptive behavior and discharge against medical advice on the part of angry and frightened patients who are in pain.

There is a fear that if patients receive narcotic analgesics, their maintenance dose of methadone might have to be increased and subsequent rehabilitation may be adversely affected. In 1980 Kantor and co-workers reported on a study comparing 25 methadone-maintained patients who were not admitted to hospital with 25 who were, with the patients then observed for a mean of 20 months.[69] They reported that whether or not large amounts of narcotic analgesics had been added to the methadone treatment regimen, they were discharged on the same methadone maintenance dose as on admission, and the eventual courses and outcomes were similar to the control group.

In the long-term administration of methadone, tolerance develops quickly to the analgesic and euphorigenic effects of methadone. This means that the established maintenance dose does not provide relief of pain. It is essential that the maintenance threshold be maintained so that additional medication can relieve pain.

Any opioid agonist can be used: meperidine hydrochloride, morphine sulfate, codeine, oxycodone, and the like. Propoxyphene is an opioid, but some physicians find its use problematic. Because of the increased tolerance, there is an apparent partial "blockade" of other opioid drugs. This simply means that doses must be adjusted for tolerance and may be required at shorter intervals. In general, pain management should be approached as in any other patient: the proper dose is enough, and the proper interval is when needed.

Mixed agonist-antagonist drugs such as pentazocine, butorphanol tartrate, nalbuphine hydrochloride, and buprenorphine hydrochloride should not be used in a person with methadone tolerance; a severe abstinence syndrome may result.

As with any patient recovering from an addictive disease, pain medication use should be discontinued as soon as practical with a substitution of nonnarcotic analgesics where possible.

## Alternatives and Adjuncts to Methadone

### *Levomethadyl Acetate*

Levomethadyl acetate (formerly levo-$\alpha$-acetylmethadol) is a long-acting narcotic replacement drug that has been extensively studied under research protocols. A single oral dose can substitute for heroin for 48 to 72 hours, reducing the need for take-home medication and associated problems of diversion. It is an orphan drug that remains in the category of an experimental drug; special legislation would be needed to make it available. There is renewed interest in it currently because it could facilitate expanding the treatment capacity of methadone. It could also be useful to patients with AIDS who do not need to enter a hospital but who are too ill to manage frequent clinic attendance. Tennant reports that the daily administration of levomethadyl acetate is helpful for patients who have low 24-hour plasma levels of methadone, suggesting potential usefulness for the subgroup of patients who do poorly even at doses of 80 to 100 mg.[70(p294)]

### *Naltrexone*

Naltrexone is a narcotic antagonist that blocks the opiate receptors so that a patient who tries heroin does not get high and is not in danger of being readdicted. It does not necessarily eliminate the craving for opiates, so the patient must be willing to explore ways of handling that experience and to identify other transitions necessary for a drug-free life-style.

Naltrexone is similar to disulfiram in that it is a tool to support abstinence while the client is engaged in a recovery program. It is useful not only to people who want to stop using opiates, but also to those who have been drug free but are experiencing difficulties and are afraid they will return to using.

Naltrexone has proved to be a disappointment for most patients because those few who seek it out do not remain in treatment for long. It appears to work best for selected populations such as health care practitioners who continue to have access to medication and for some parolees and probationers. Retention in the absence of some form of therapeutic coercion is poor, possibly owing to dysphoria because the natural opioids are blocked.[71]

Dole, from the perspective of the receptor derangement theory, thinks that the lack of success with naltrexone is due to the fact that it is pharmacologically wrong:

> Antagonist drugs block the action of natural ligands as well as that of illicit narcotics. If the basic problem leading to relapse is a failure of the modulating system to return to normal function after withdrawal of narcotic, then antagonist treatment adds to the problem.[12(p3028)]

Naltrexone appears useful in accelerating the withdrawal process for patients undergoing detoxification using clonidine hydrochloride. These patients get sicker for a few hours, but it is over quickly and seems to reduce the severity of the chronic or delayed abstinence syndrome. These patients return to full function faster and are protected from immediate relapse. Of those who at least get through a naltrexone induc-

tion after withdrawal from methadone, few (sadly) stay with it more than a week or so.

*Buprenorphine Hydrochloride*

Buprenorphine hydrochloride is a mixed-opioid agonist-antagonist that has suppressed opioid use by heroin addicts.[72] It is also being researched for heroin detoxification and is considered somewhat safer than methadone for this purpose; because there is a ceiling on its ability to cause respiratory depression, overdoses are less likely to cause death.[73(p276)] Recently interest has centered on its effectiveness in suppressing cocaine use. Mello and associates report that the daily administration of buprenorphine substantially suppressed cocaine self-administration by rhesus monkeys.[74] Because of the risk of creating a new opioid dependence, many substance abuse practitioners are concerned about this application in patients who use cocaine but not opioids. Human subjects studied so far have been opioid abusers, not purely cocaine addicts, but buprenorphine may be a promising agent for patients dually addicted to opioids and cocaine and for patients on methadone maintenance who also use cocaine. Kosten and co-workers studied 130 opioid addicts who were "speedballing" (combining opioids with cocaine) and found that buprenorphine significantly reduced cocaine use in this population.[75]

*Clonidine for Detoxification From Heroin and Methadone*

Clonidine is an $\alpha_2$-adrenergic agonist that can be given to control many of the symptoms of narcotic withdrawal.[76] The opiate withdrawal syndrome is characterized by an enormous burst of sympathetic overactivity. The mechanism of action of clonidine is central $\alpha$-adrenergic stimulation, resulting in an inhibiton of peripheral sympathetic discharge.

The proper use of clonidine can result in a pronounced reduction, but not elimination, of opiate withdrawal signs and symptoms. There is considerable variation in individual sensitivity to the various effects of clonidine. Individual titration of doses is based on the monitoring of blood pressure, side effects, and severity of the abstinence syndrome.

Clonidine therapy offers a notable advantage by providing considerable relief of the abstinence syndrome without interfering with the duration of withdrawal. Methadone and other opioids, on the other hand, provide relief by stopping or slowing the withdrawal process. Therefore, clonidine-treated opioid withdrawal—assuming an abrupt opioid cessation—is similar in duration to "cold-turkey" withdrawal.[77] This limits the clinical usefulness of clonidine.

Withdrawal from methadone is less intense but longer in duration than that from shorter-acting opioid agonists such as heroin. The prolonged acute withdrawal is then followed by several months of what has been variously described as a chronic or delayed abstinence syndrome or "postmethadone syndrome," described earlier in this article.

One solution is the combined use of naltrexone and clonidine, which provides a rapid, safe, and relatively comfortable transition from methadone maintenance (or other opioid dependence) to naltrexone maintenance. The process can be accomplished in as little as 24 hours to as much as 10 to 14 days. Charney and associates report on their procedure that allowed 38 of 40 patients addicted to methadone to be withdrawn completely in four or five days.[78]

The initial dose of oral clonidine is usually 5 $\mu$g per kilogram of body weight, which is then repeated at six hours, eight hours, or as needed, after which the dose should be titrated on an individual basis.[78] Clonidine in the form of transdermal patches (Catapres-TTS) offers the advantages of improved steady-state clonidine levels and less oral medication, which is especially attractive in outpatient protocols. Clark and Longmuir recommend the use of two No. 2 patches (0.4 mg per day) if the patient weighs less than 68 kg (150 lb), three No.2 or two No. 3 patches (0.6 mg per day) if the weight is more than 68 kg. Small amounts of oral clonidine may be used to "fine tune" the clonidine effect.[79]

During the naltrexone-induction phase, clonidine doses may be increased to as much as 0.6 mg every four hours in response to the accelerated withdrawal. As the dose of naltrexone reaches maintenance levels (50 mg per day), the clonidine dose may be reduced rapidly (a graded reduction over two to three days is preferred), indicating that withdrawal is essentially complete. The transition now being complete, the patient enters the naltrexone maintenance phase. Having achieved a drug-free state, the real task begins in the effort to maintain this state. There is no evidence that any withdrawal technique has any significant influence on long-term abstinence.

## Methadone-Maintained Patients in 12-Step Programs

The changing climate surrounding methadone treatment has resulted in patients on methadone maintenance using 12-step programs more frequently. Patients have found their way to meetings, initially to address their alcohol problems, and spread the word that they were helpful. Some programs encouraged participation,[80] not only to provide a resource to address alcoholism and drug use, but as a way of generating a support system of nonusers as a preparation for stopping methadone therapy. In addition, many patients are able and eager to use the 12-step recovery process for ongoing personal development, in the place of or in addition to counseling offered in the program. Twelve-step meetings for patients on methadone maintenance are available in certain geographic locations. Information about these should be available from local programs.

## Conclusion—The Growing Legitimacy of Methadone Treatment

There is little doubt there is a critical need to expand and improve treatment of heroin addiction, with the goal of providing treatment for all who seek it. In any given community, this means providing a range of treatment options, of which methadone maintenance is a legitimate choice. Various barriers must be removed to make treatment acceptable to practicing addicts. The methadone treatment method has repeatedly been shown to be safe and effective, though political considerations may stimulate redundant evaluations.

At the level of individual programs, great differences in effectiveness exist. Ball and many others such as the groups at Yale and in Philadelphia are seeking to identify the elements of effective treatment of different populations,[41] which is essential to the process of improving quality of care. At the federal level, attention is shifting toward the development and use of performance-based standards of care for methadone treatment programs. Many hope that the various state methadone authorities will follow this example.

Leadership is currently being provided by several professional groups. The American Society of Addiction Medicine

(ASAM), formerly the American Society on Alcoholism and Other Drug Dependencies, in 1989 marked its 35th anniversary as an organization. This organization is the force behind the emerging medical specialty known as addiction medicine, with the goal of attaining specialty board status for the specialty. The current membership exceeds 3,600 physicians, about half of whom are certified by examination.

In 1987 David E. Smith, MD, proposed that a committee be established to bring methadone treatment into the family of addiction medicine, and this committee has since been actively attending to key issues in the field. During 1989 and 1990, ASAM responded to proposed rule changes on the part of NIDA and FDA related to an interim treatment concept and the development of the performance-based standards of care. It has focused extensively on education, which is critical to ensure that methadone treatment can evolve in such a way as to meet the present and future needs. Educational efforts are targeted to the field of chemical dependence itself, mainstream medicine and health care, the general public, and to governmental agencies at all levels. Work is beginning on developing standards of care and criteria for admission, continued treatment (at various levels or intensities of care), and discharge or transfer. In the words of Jasper G. Chen See, MD, president of ASAM, "Our objective has always been the upgrading of skills and improvement of knowledge leading to better patient care."

Another important force in the field is the Northeast Regional Methadone Treatment Coalition, Inc (New York City), which will meet in March of 1991 as the National Methadone Treatment Coalition. While sharing concerns with ASAM for quality of care and the availability of treatment issues, it is unique in having a narrower focus (specifically concerned with methadone treatment) and broader participation involving all levels of staff from administrators to nurses and counselors.

It would seem that methadone treatment has survived a difficult period of growth and development to now be perceived as a legitimate and critical resource in the struggle against intravenous drug abuse and AIDS. Much work remains to be done as the methadone treatment field enters a phase of maturation and refinement. New resources and strong networks for collaboration hold a promise of steady progress on these challenging tasks.

## REFERENCES


1. Hunt DE, Lipton DS, Goldsmith DS, et al: 'It takes your heart': The image of methadone maintenance in the addict world and its effect on recruitment into treatment. Int J Addict 1985; 20:1751-1771

2. Stark MJ: A psychoeducational approach to methadone maintenance treatment. J Subst Abuse Treat 1989; 6:169-181

3. Senay EC: Methadone maintenance treatment. Int J Addict 1985; 20:803-821

4. Cooper JR, Altman F, Brown BS, et al: Research on the Treatment of Narcotic Addiction. Washington, DC, Government Printing Office, 1983

5. Tims FM, Ludford JP: Drug Abuse Treatment Evaluation: Strategies, Process and Prospects. Rockville, Md, National Institute on Drug Abuse (NIDA), US Dept of Health and Human Services, 1984

6. Hubbard RL, Marsden ME, Rachal JV, et al: Drug Abuse Treatment: A National Study of Effectiveness. Chapel Hill, NC, University of North Carolina Press, 1989

7. Drug Use in America: Problem in Perspective—Second Report of the National Commission on Marijuana and Drug Abuse. Washington, DC, Government Printing Office, 1973

8. Zweben JE: Recovery oriented psychotherapy. J Subst Abuse Treat 1986; 3:255-262

9. Zweben JE, Sorenson J: Misunderstandings about methadone. J Psychoactive Drugs 1988; 3:275-281

10. Dole V, Nyswander M: Methadone maintenance: A theoretical perspective. *In* Lettieri DJ, Sayers M, Pearson HW (Eds): Theories on Drug Abuse: Selected Contemporary Perspectives. Rockville, Md, NIDA, US Dept of Health and Human Services, 1980

11. Dole V, Nyswander M: Heroin addiction: A metabolic disease. Arch Intern Med 1967; 120:19-24

12. Dole V: Implications of methadone maintenance for theories of narcotic addiction. JAMA 1988; 260:3025-3029

13. Kreek MJ: Tolerance and dependence: Implications for the pharmacological treatment of addiction, *In* Harris LS (Ed): Problems of Drug Dependence, 1986. Proceedings of the 48th Annual Scientific Meeting of the Committee on Problems of Drug Dependence, DHHS publication No. (ADM) 87-1508. Rockville, Md, NIDA, US Dept of Health and Human Services, 1986, pp 53-62

14. Jaffe JH, Martin WR: Opioid analgesics and antagonists, chap 22, *In* Gilman AG, Goodman LS, Rall TW, et al (Eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 6th Ed. New York, Macmillan, 1980, pp 494-534

15. Dole VP, Kreek MJ: Methadone plasma level: Sustained by a reservoir of drug in tissue. Proc Natl Acad Sci 1973; 70:10

16. Kreek MJ: Methadone in treatment: Physiological and pharmacological issues, *In* Dupont RI, Goldstein A, O'Donnell J (Eds): Handbook on Drug Abuse. Rockville, Md, NIDA, US Dept of Health and Human Services, 1979, pp 57-85

17. Hargreaves WA: Methadone dose and duration for maintenance treatment, *In* Cooper JR, Altman F, Brown BS, et al (Eds): Research on the Treatment of Narcotic Addiction: State of the Art, publication No. (ADM) 83-1281. Rockville, Md, NIDA, US Dept of Health and Human Services, 1983, pp 19-79

18. Dole V: Addictive behavior. Sci Am 1980; 243:138-157

19. Tennant F: Inadequate plasma concentration in some high-dose methadone maintenance patients. Am J Psychiatry 1987; 144:1349-1350

20. McLellan AT: Patient characteristics associated with outcome, *In* Cooper JR, Altman F, Brown BS, et al (Eds): Research on the Treatment of Narcotic Addiction: State of the Art, publication No. (ADM) 83-1281. Rockville, Md, NIDA, US Dept of Health and Human Services, 1983, pp 500-523

21. Cushman P: Detoxification after methadone treatment, *In* Lowinson JH, Ruiz P (Eds): Substance Abuse: Clinical Problems and Perspectives. Baltimore, Williams & Wilkins, 1981, pp 389-395

22. Gold ML, Sorensen JL, McCanlies N, et al: Tapering from methadone maintenance: Attitudes of patients and staff. J Subst Abuse Treat 1988; 5:37-44

23. Sorensen JL, Deitch DA, Acampora A: Treatment collaboration of methadone maintenance programs and therapeutic communities. Am J Drug Alcohol Abuse 1984; 10:347-359

24. Wermuth L, Brummett S, Sorensen JL: Bridges and barriers to recovery: Clinical observations from an opiate recovery project. J Subst Abuse Treat 1987; 4:189-196

25. Milby JB, Gurwitch RH, Wiebe DJ, et al: Prevalence and diagnostic reliability of methadone maintenance detoxification fear. Am J Psychiatry 1986; 143:739-743

26. Rosenbaum M, Murphy S, Beck J: Money for methadone: Preliminary findings from a study of Alameda County's new maintenance policy. J Psychoactive Drugs 1987; 19:13-19

27. Newman RG: Methadone treatment: Defining and evaluating success. N Engl J Med 1987; 317:447-450

28. Lowinson JH: Methadone maintenance in perspective, *In* Lowinson JH, Ruiz P (Eds): Substance Abuse: Clinical Problems and Perspectives. Baltimore, Williams & Wilkins, 1981, pp 344-354

29. National Institute on Drug Abuse: Effectiveness of Drug Abuse Treatment Programs. Washington, DC, Government Printing Office, 1981

30. Blinick G, Jerez E, Wallach RC: Methadone maintenance, pregnancy, and progeny. JAMA 1973; 225:477-479

31. Zuspan FP, Gumpel JA, Mejia-Zelaya A, et al: Fetal stress from methadone withdrawal. Am J Obstet Gynecol 1975; 122:43-46

32. Stimmel B, Goldberg J, Reisman A, et al: Fetal outcome in narcotic-dependent women: The importance of the type of maternal narcotic used. Am J Drug Alcohol Abuse 1982; 9:383-395

33. Doberczak TM, Thornton JC, Bernstein J, et al: Impact of maternal drug dependency on birth weight and head circumference of offspring. Am J Dis Child 1987; 141:1163-1167

34. Kaltenbach K, Finnegan LP: Perinatal and developmental outcome of infants exposed to methadone in-utero, *In* Harris LS (Ed): Problems of Drug Dependency, 1986. Proceedings of the 48th Annual Scientific Meeting of the Committee on Problems of Drug Dependence, DHHS publication No. (ADM) 87-1508. Rockville, Md, NIDA, US Dept of Health and Human Services, 1987

35. Pond SM, Kreek MJ, Tong TG, et al: Altered methadone pharmacokinetics in methadone-maintained pregnant women. J Pharmacol Exp Ther 1985; 233:1-6

36. Finnegan LP: Neonatal abstinence syndrome: Assessment and pharmacotherapy, *In* Rubaltelli FF, Granati B (Eds): Neonatal Therapy: An Update. New York, Elsevier Science, 1986

37. Hubbard RL, Marsden ME, Cavanaugh E, et al: Role of drug-abuse treatment in limiting the spread of AIDS. Rev Infect Dis 1988; 10:377-384

38. Batki S: Treatment of intravenous drug users with AIDS: The role of methadone maintenance. J Psychoactive Drugs 1988; 20:213-216

39. Effectiveness of Drug Abuse Treatment as an AIDS-Prevention Strategy. American Society on Alcoholism and Other Drug Dependencies 3rd National Forum on AIDS and Chemical Dependency: Integrating AIDS Prevention and Treatment With Chemical Dependency Treatment, February 1989, Miami

40. Bourne PG: AIDS and drug use: An international perspective. J Psychoactive Drugs 1988; 20:153-157

41. Ball JC, Lange WR, Myers CP, et al: Reducing the risk of AIDS through methadone maintenance treatment. J Health Social Behav 1988; 29:214-226

42. Faith RE, Plotnikoff NP, Murgo AJ: Effects of opiates and neuropeptides on immune functions, *In* Sharp WC (Ed): Mechanisms of Tolerance and Dependence. Rockville, Md, NIDA, US Dept of Health and Human Services, 1984

43. Falek A, Madden JJ, Shafer DA, et al: Individual differences in opiate-induced alterations at the cytogenetic, DNA repair, and immunological levels: Opportunity for genetic assessment, *In* Braude MC, Chao HM (Eds): Genetic and Biological Markers

in Drug Abuse and Alcoholism. Rockville, Md, NIDA, US Dept of Health and Human Services, 1986

44. Lazzarin A, Mella L, Trombini M, et al: Immunological status in heroin addicts: Effects of methadone maintenance treatment. Drug Alcohol Depend 1984; 13:117-123

45. Novick DM, Kreek MJ, Arns PA, et al: Effect of severe alcoholic liver disease on the disposition of methadone in maintenance patients. Alcoholism (NY) 1985; 9:349-354

46. Novick DM, Ochshorn M, Ghali V, et al: Natural killer cell activity and lymphocyte subsets in parenteral heroin abusers and long-term methadone maintenance patients. J Pharmacol Exp Ther 1989; 250:606-610

47. Sorensen JL, Batki S, Good P, et al: Methadone maintenance program for AIDS-affected opiate addicts. J Subst Abuse Treat 1989; 6:87-94

48. Wallen H, Weiner H: Impediments to effective treatment of the dually diagnosed patient. J Psychoactive Drugs 1988; 21:161-168

49. Wallace J: The other problems of alcoholics. J Subst Abuse Treat 1986; 3:163-171

50. Mirin S (Ed): Substance Abuse and Psychopathology. Washington, DC, American Psychiatric Press, 1984

51. Meyer RE (Ed): Psychopathology and Addictive Disorders. New York, Guilford Press, 1986

52. Berken GH, Stone MM, Stone SK: Methadone in schizophrenic rage: A case study. Am J Psychiatry 1978; 135:248-249

53. Brizer DA, Hartman N, Sweeney J, et al: Effect of methadone plus neuroleptics on treatment-resistant chronic paranoid schizophrenia. Am J Psychiatry 1985; 142:1106-1107

54. Comfort A: Morphine as an antipsychotic. Lancet 1977; 2:443-444

55. Kleber H: Is there a need for 'professional psychotherapy' in methadone programs? J Subst Abuse Treat 1984; 1:73-76

56. Woody GE, Luborsky L, McLellan AT, et al: Psychotherapy for opiate addicts—Does it help? Arch Gen Psychiatry 1983; 40:639-645

57. Anglin MD, Almog IJ, Fisher DG, et al: Alcohol use by heroin addicts: Evidence for an inverse relationship—A study of methadone maintenance and drug-free treatment samples. Am J Drug Alcohol Abuse 1989; 15:191-207

58. Gordis E: Methadone maintenance and patients in alcoholism treatment. Natl Inst Alcohol Abuse Alcohol Alert 1988; 1:1-4

59. Bickel WK, Marion I, Lowinson JH: The treatment of alcoholic methadone patients: A review. J Subst Abuse Treat 1987; 4:15-19

60. Novick DM, Stenger RJ, Gelb AM, et al: Chronic liver disease in abusers of alcohol and parenteral drugs: A report of 204 consecutive biopsy-proven cases. Alcoholism (NY) 1986; 10:500-505

61. Kosten TR, Rounsaville BJ, Kleber HD: Antecedents and consequences of cocaine use among opioid addicts—A 2.5 year follow up. J Nerv Mental Dis 1988; 176:176-181

62. Hanbury R, Sturiano V, Cohen M, et al: Cocaine use in persons on methadone maintenance. Adv Alcohol Subst Abuse 1986; 6:97-106

63. Stitzer ML, Griffiths RR, McLellan AT, et al: Diazepam use among methadone maintenance patients: Patterns and dosages. Drug Alcohol Depend 1981; 8:189-199

64. Smith DE, Wesson DR: Benzodiazepine dependency syndromes, *In* The Benzodiazepines: Current Standards for Clinical Practice. Boston, MTP Press, 1985, pp 235-248

65. Saxon AJ, Whittaker S, Hawker CS: Valproic acid, unlike other anticonvulsants, has no effect on methadone metabolism: Two cases. J Clin Psychol 1989; 50:228-229

66. Baciewicz AM, Self TH, Bekemeyer WB: Update on rifampin drug interactions. Arch Intern Med 1987; 147:565-568

67. O'Brien CP, Childress AR, Arndt IO, et al: Pharmacological and behavioral treatments of cocaine dependence: Controlled studies. J Clin Psychol 1988; 49:17-22

68. Liu SJ, Wang RI: Case report of barbiturate-induced enhancement of methadone metabolism and withdrawal syndrome. Am J Psychiatry 1984; 141:1287-1288

69. Kantor TG, Cantor R, Tom E: A study of hospitalized surgical patients on methadone maintenance. Drug Alcohol Depend 1980; 6:163-173

70. Tennant F: LAAM maintenance for opioid addicts who cannot maintain with methadone, *In* Harris LS (Ed): Problems of Drug Dependence, 1987. Proceedings of the 49th Annual Scientific Meeting of the Committee on Problems of Drug Dependence, DHHS publication No. (ADM) 88-1564. Rockville, Md, NIDA, US Dept of Health and Human Services, 1988

71. Crowley TJ, Wagner JE, Zerbe G, et al: Naltrexone-induced dysphoria in former opioid addicts. Am J Psychiatry 1985; 142:1081-1084

72. Mello NK, Mendelson JH: Behavioral pharmacology of buprenorphine. Drug Alcohol Depend 1985; 14:283-303

73. Bickel WK, Johnson RE, Stitzer ML, et al: A clinical trial of buprenorphine: I. Comparison with methadone in the detoxification of heroin addicts; II. Examination of its opioid blocking properties, *In* Harris LS (Ed): Problems of Drug Dependence, 1986. Proceedings of the 48th Annual Scientific Meeting of the Committee on Problems of Drug Dependence, DHHS publication No. (ADM) 87-1508. Rockville, Md, NIDA, US Dept of Health and Human Services, 1987

74. Mello NK, Mendelson JH, Bree MP, et al: Buprenorphine suppresses cocaine self-administration by rhesus monkeys. Science 1989; 245:859-862

75. Kosten TR, Kleber HD, Morgan C: Role of opioid antagonists in treating intravenous cocaine abuse. Life Sci 1989; 44:887-892

76. Cohen S: Clonidine (Catapres): Nonopiate detoxification. Drug Abuse Alcohol Newsletter 1980 Jul;

77. Roehrich H, Gold MS: Clonidine. Adv Alcohol Subst Abuse 1987; 7:1-16

78. Charney DS, Heninger GR, Kleber HD: The combined use of clonidine and naltrexone as a rapid, safe, and effective treatment of abrupt withdrawal from methadone. Am J Psychiatry 1986; 143:831-837

79. Clark HW, Longmuir N: Clonidine transdermal patches: A recovery oriented treatment of opiate withdrawal. Calif Soc Treat Alcohol Drug Depend News 1986; 13:1-2

80. Obuchowsky M, Zweben J: Bridging the gap: The methadone patient in 12-step programs. J Psychoactive Drugs 1987; 19:301-302

**Addiction Medicine**
**and the Primary Care Physician**

# A Physician's Guide to Discontinuing Benzodiazepine Therapy

ROBERT L. DuPONT, MD, *Rockville, Maryland*

*Practicing physicians need to have practical techniques to help patients who want to stop using benzodiazepines. I have developed three approaches that usually work. The first, and most widely applicable, is gradually reducing the dose without adding any other medicine. Failing this, use one of the following two approaches, occasionally combining them: switch to a longer-acting, cross-tolerant medication (usually clonazepam or phenobarbital) or use medications to suppress the withdrawal symptoms, usually carbamazepine, propranolol, or clonidine. If this fails, use inpatient detoxification. Chemically dependent patients, including those abusing alcohol and taking higher than recommended doses of sedative-hypnotics, require special care during discontinuation. Aftercare is important for all long-term benzodiazepine users if they are to remain drug-free and live relatively comfortable lives.*

(DuPont RL: A physician's guide to discontinuing benzodiazepine therapy, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:600-603)

When the benzodiazepines were introduced in the early 1960s as "tranquilizers," they were welcomed as something only slightly less than miracle medicines. The strong counterreactions to their widespread use in the 1970s led to roughly a 25% drop in the number of prescriptions written for these medicines and a shift in prevailing views of the public and of medicine so that today they are the most controversial of all psychotropic medicines.[1,2]

In recent years the increasing use of shorter-acting benzodiazepines such as lorazepam (Ativan), alprazolam (Xanax), and triazolam (Halcion) has combined with the increasing use of the benzodiazepines to treat more seriously ill patients to create a new concern about withdrawal, even from routine therapeutic doses.[3] This heightened concern has been reinforced by the growing familiarity of physicians with the problems of chemical dependency.

## Identifying the Need to Discontinue Benzodiazepine Therapy

Approximately 3 million Americans (1.6% of the adult population) have used a benzodiazepine on a daily basis for at least 12 months.[4] Some of these patients want help from their physicians in discontinuing the medication. Other patients, some of whom do not want to stop using a benzodiazepine, nevertheless should have their therapy discontinued. Many actively chemically dependent patients need help becoming drug-free, and sometimes benzodiazepines are part of their overall drug-dependence problem. In this article I focus on how physicians can help patients who want to stop using benzodiazepines achieve that goal.

There are many patients who use the medicine with substantial benefit who do not want to stop. Occasionally physicians become zealous in convincing these patients to stop the use of benzodiazepines. Surely patient desire to stop benzodiazepine use is almost always an adequate reason for a physician to help the patient stop using the medicine, but what if the patient does not want to stop?

There are four circumstances in which urging a patient to stop taking benzodiazepines is usually justified.

- The patient has an active chemical dependence, including the use of alcohol in amounts greater than four drinks a week and any continuing use of illicit drugs, including marijuana or cocaine.
- The benzodiazepine dose is above what the Food and Drug Administration recommends for anxiety, except in the treatment of panic disorder when higher doses are sometimes needed, especially early in treatment.
- The patient has a poor therapeutic response.
- The patient is showing toxic behavior, including signs of sedation, impairment, and treatment-related mental disorders such as depression.

A patient who uses illicit drugs, such as marijuana or cocaine, on a continuing basis, and any patient who drinks excessively, should not use benzodiazepines. Excessive drinking, for these purposes, means four or more drinks a week and any episode of intoxication in the past year. Such patients generally do poorly on benzodiazepine therapy. The possibility of the drug contributing to the chemical dependency tips the risk-benefit calculation toward discontinuing its use.

Second, when the benzodiazepine dose is higher than the usual maximum dose, consideration should be given to discontinuing the therapy except in the treatment of panic disorder, especially early in the treatment, when higher doses may be needed (Table 1). Most anxious patients are successfully treated at doses equal to or less than half the maximum usual dose. Most patients with psychophysiologic disorders of initiating and maintaining sleep, or anxious insomnia, are successfully treated with benzodiazepine doses not exceeding

From the Institute for Behavior and Health, Rockville, Md, and the Department of Psychiatry, Georgetown University School of Medicine, Washington, DC.
Reprint requests to Robert L. DuPont, MD, President, Institute for Behavior and Health, Inc, 6191 Executive Blvd, Rockville, MD 20852.

the maximum usual doses with no evidence of tolerance—that is, dosage escalation or loss of efficacy over time.

Third, any patient who has a poor therapeutic response to a benzodiazepine is a candidate for discontinuation. Most anxious patients, without chemical dependency, respond well to this drug therapy at low, stable doses without dosage escalation or loss of efficacy even over long periods of time.

Fourth, any patient who shows toxic behavior or impairment should also be encouraged to discontinue using the medicine. Typical problems that may be caused by benzodiazepine use are slurred speech or staggering (indicating sedation), accidents, and treatment-related emotional lability or depression.

If a patient taking benzodiazepines over a long period of time wants to continue using the medicine, uses a moderate dose with a good therapeutic response, and fails to show chemical dependence or impairment, then that patient can continue taking the medicine for years or even for a lifetime.

Many physicians who are unfamiliar with the newer understanding of anxiety disorders—that they are both common and often crippling, biologically based disorders—can easily misperceive such patient desire to continue using a benzodiazepine as "drug dependence" when it is more realistically a rational response by the patient to a good therapeutic result for a serious illness.[5,6]

## Basic Plan for Outpatient Discontinuation

Most patients seeking benzodiazepine discontinuation suffer from anxiety disorders. They are chronic "worriers" who have spent years "borrowing trouble" in their lives. As one chronically anxious patient said to me, "I have had a terrible life, but most of it never happened." This tendency to worry and to focus on the worst possible outcomes makes discontinuing benzodiazepine use more difficult for these patients because they are likely to have symptoms of withdrawal as well as of relapse of their treated anxiety disorder. Anxious patients worry excessively about discontinuing benzodiazepine and the symptoms they will have. Their inappropriate worries can be unintentionally increased by a worried physician. The physician needs to be calm and confident about the process of discontinuation, as well as realistic and sympathetic about the distress the patient can expect. I usually tell my patients that their symptoms will be "distressing but not dangerous" and that the symptoms will become most intense at the lowest dose levels, peaking in the first week or two after they are completely off all benzodiazepine therapy.[7] Patients find it reassuring to know the upsurge of symptoms is not dangerous and that it will fade if they stick with the discontinuation protocol. I also tell the patients that we can make the discontinuation as long (up to about three or four months) or as short (but not less than two or three weeks) as the patient wants, with the understanding that longer time periods mean more prolonged but less intense discontinuation symptoms.

Once the patient and the physician have determined that benzodiazepine discontinuation is desirable, it is usually best to structure a gradual outpatient discontinuation schedule over 6 to 12 weeks using the same medicine the patient has been taking. Most patients cannot take physicians' advice to "gradually cut down the dose." It is helpful to work with the patient to structure each dose over the entire period of discontinuation by writing down when each dose should be taken. Usually it is also helpful to give patients permission to use a small "extra dose" on any day they feel a special need for extra help. This helps them to feel in control. I also encourage patients to come in for office visits once a week during this period, and I give them my home telephone number in case they have any particular problems. Although patients seldom call, having my phone number is reassuring to them. I also give the patient a booklet about benzodiazepine discontinuation to refer to and to share with other family members.[8]

It is sometimes useful during the benzodiazepine discontinuation period to administer an unrelated medicine that has some antianxiety properties. Antidepressants are helpful, especially desipramine hydrochloride and fluoxetine. They are especially useful for patients suffering from panic disorder, depression, or both. If the patient is not already taking one of these medicines before discontinuing the benzodiazepine therapy, it can be started about a month before the benzodiazepine dose reduction begins. The antidepressant therapy can be continued for at least two months after the last benzo-

TABLE 1.—*Pharmacologic Characteristics of Benzodiazepines*

| *Drug* | *Trade Names** | *Rate of Oral Absorption* | *Rate of Metabolism* | *Metabolized Primarily By Liver Oxidation* | *Active Metabolites* | *Elimination ½-Life, h* | *Maximum Usual Dose, mg/d* |
|---|---|---|---|---|---|---|---|
| *Used primarily to treat anxiety* | | | | | | | |
| Alprazolam | Xanax | Intermediate | Intermediate | Yes | Yes | 12-15 | 4 |
| Chlordiazepoxide HCl | Librium | Intermediate | Long | Yes | Yes | 5-30 | 100 |
| Clonazepam | Klonopin | Fast | Long | Yes | No | 18-50 | 2 |
| Clorazepate dipotassium | Tranxene | Fast | Long | Yes | Yes | 36-200 | 60 |
| Diazepam | Valium | Fast | Long | Yes | Yes | 20-50 | 40 |
| Halazepam | Paxipam | Intermediate | Long | Yes | Yes | 50-100 | 160 |
| Lorazepam | Ativan | Intermediate | Short | No | No | 10-14 | 10 |
| Oxazepam | Serax | Slow | Short | No | No | 5-10 | 120 |
| Prazepam | Centrax | Slow | Long | Yes | Yes | 36-200 | 60 |
| *Used primarily to treat insomnia* | | | | | | | |
| Flurazepam HCl | Dalmane | Intermediate | Long | Yes | Yes | 40-150 | 30 |
| Temazepam | Restoril | Intermediate | Short | No | Yes | 8-12 | 30 |
| Triazolam | Halcion | Intermediate | Short | Yes | No | 2-5 | 0.25 |

HCl=hydrochloride

*Some of the drugs are manufactured by more than one company. The names given here are examples only and do not imply endorsement by the author or the editors of THE WESTERN JOURNAL OF MEDICINE.

diazepine dose, gradually reducing the dose of the antidepressant over a month or longer.

Discontinuing the antidepressant therapy can also be a problem because of the upsurge of symptoms of the underlying anxiety disorder, but it is unlikely to produce the rebound or withdrawal symptoms that sometimes occur on discontinuing benzodiazepine use.[9]

## Back-up Plan for Discontinuing Benzodiazepine Therapy

While the basic plan often works, sometimes other measures are needed. Actively chemically dependent patients usually cannot stop benzodiazepine and other psychoactive medicine use with this simple outpatient approach. They usually need referral to a chemical dependence treatment program, either outpatient or inpatient, and referral to a 12-step program such as Alcoholics Anonymous or Narcotics Anonymous. Family members should be referred to Al-Anon.

Patients who are not chemically dependent sometimes cannot complete the basic plan. The simplest supplement is to switch the drug that is currently being used to a longer-acting cross-tolerant substance, such as clonazepam (Klonopin) or phenobarbital.[10-12] For patients who are using the usual therapeutic doses of benzodiazepines, this commonly means 0.5 mg of clonazepam at bedtime, if needed, and the same dose in the morning. An alternative to 0.5 mg of clonazepam is 30 mg of phenobarbital. Some patients who are using higher doses may need more medication, but because sedation is the most common side effect of both clonazepam and phenobarbital, it is usually possible to work with a patient to find a dose that is sufficient to prevent most discomfort without being unpleasantly sedating. Having established the dose of clonazepam or phenobarbital, that dose is continued for a week, during which the patient can take up to the level of benzodiazepine used before switching to the new medicine, but using the benzodiazepine only as needed.

For example, if a patient is taking 0.5 mg of alprazolam three times a day at the start of the switch and takes 0.5 mg of clonazepam at bedtime, then he or she can use as much as 0.5 mg of alprazolam three times a day for one week on an "as-needed" basis. After that week the clonazepam blood concentration is high enough that no further alprazolam is needed. If the patient is uncomfortable when stopping the alprazolam use, then the clonazepam dose can be increased temporarily. Having made the switch to clonazepam, the dose of that medicine is reduced by half a tablet every week or two. Phenobarbital can be used the same way, with 30 mg of phenobarbital substituted for 0.5 mg of clonazepam.

If this approach fails, the physician can try to suppress the symptoms of withdrawal by one of three approaches, all still experimental at this time. First, propranolol hydrochloride (Inderal), 20 mg up to three or four times a day, can be used for a week before reaching a zero benzodiazepine dose and for two weeks thereafter. Second, clonidine hydrochloride (Catapres) can be used orally in doses of 0.1 mg as much as four to six times a day as tolerated for a week before and two weeks after achieving zero dose. An alternative approach to oral clonidine use is the skin patch. Usually a #2 patch (designed to provide 0.2 mg of clonidine per day) is applied for a week before reaching a zero benzodiazepine dose and for a week or two after. This approach with clonidine patches has been used extensively in suppressing nicotine withdrawal from cigarette smoking cessation.[13]

Third, carbamazepine can be used for two weeks before reaching a zero benzodiazepine dose, with the starting dose of 200 mg twice a day raised gradually to 800 mg a day, or as much as the patient can tolerate. The dose of carbamazepine is then continued until the patient is off the benzodiazepine therapy for one or two weeks. In all three of these approaches, patients are best served by getting to the lowest benzodiazepine dose they can tolerate before starting the withdrawal-suppressing medicine. The final doses of the benzodiazepine should be gradually discontinued over one or two weeks under the "cover" of the additional medicine.

All three of these approaches have drawbacks. Clonidine and propranolol cause drops in blood pressure, which can be disturbing and even dangerous. Carbamazepine can cause a drop in the leukocyte count, which may be fatal. All three medicines commonly cause sedation. These three approaches are most easily used in inpatient treatment when there is less danger from sedation and blood pressure drops and when it is easier to manage the patients, but they can be used in outpatient settings with careful supervision.

Finally, if these approaches fail to help the patient reach a zero dose of the benzodiazepine, inpatient treatment is indicated, which, in my experience, is always successful.

## Life Without Benzodiazepine

Once the benzodiazepine-free goal of therapy is achieved, the real challenge begins. Typically these patients have many continuing symptoms of anxiety disorder, which is why they started and continued using benzodiazepines. It is important to help the patient find ways to deal with the distress of the underlying illness without using one of these medicines. Various options can be considered. Antidepressants, particularly fluoxetine and desipramine, are often good choices. Some anxious patients with and without depression do well on relatively low doses of these medicines (such as 25 mg a day of desipramine or 10 mg of fluoxetine). Buspirone hydrochloride (BuSpar) is a rational alternative to a benzodiazepine for anxious patients. Unlike the antidepressants, it does not suppress panic attacks or treat depression. Because of its apparently low antianxiety efficacy, I have not had much success with buspirone, particularly in patients who have previously used benzodiazepine. The antidepressants and buspirone take several weeks to develop efficacy.

In addition, there are a variety of nonpharmacologic treatments of anxiety that are worth trying. Some patients do well with the new cognitive-behavioral therapy commonly available in the modern phobia- or anxiety-treatment clinic. Other patients do well with books that offer help in understanding and coping with the underlying anxiety disorder. Claire Weekes's books are particularly helpful.[14-17]

Anxious patients often do well with aerobic exercise programs and with courses teaching assertiveness and relaxation. They may also benefit from traditional psychotherapy or from therapy focusing on marital or other family problems that may underlie their distress.

The point of this review of patients' options is to encourage physicians to emphasize to patients that there are many choices the patients have to cope with their problems of anxiety and insomnia, the primary problems that lead to taking benzodiazepines over long periods of time.

Some patients who do not have ongoing chemical depen-

dence problems, and all who do, should be referred to a 12-step program, some of which focus on "pills," including the benzodiazepines. This can be disturbing to the physician because these mutual-aid groups sometimes consider the physician a "pusher" for giving a patient a prescription for long periods of time.

## Conclusions

The benzodiazepines are good medicines for anxiety. They are safe and effective. There are two primary problems that confront physicians using these medicines: abuse by chemically dependent people and difficult discontinuation. There are simple, practical ways physicians can help their patients stop using benzodiazepines.

Not every patient taking one of these drugs for prolonged periods of time should have their therapy involuntarily discontinued. These medicines do not generally lose their anti-anxiety effectiveness over time. They are safe, even for prolonged use. On the other hand, many patients want help getting off the medication therapy. Some patients who want to take them have problems that make discontinuation prudent. Using the guidelines in this article, it is possible for most physicians to use these medicines with confidence and to cope effectively with the problems that do develop on occasion.

### REFERENCES

1. DuPont RL: Benzodiazepines: The Social Issues. Rockville, Md, Institute for Behavior and Health, 1986

2. DuPont RL (Ed): Abuse of benzodiazepines: The problems and the solutions. Am J Drug Alcohol Abuse 1989; 14(Suppl 1)

3. DuPont RL: A practical approach to benzodiazepine discontinuation. J Psychiatr Res, in press

4. Mellinger GD, Balter MB: Prevalence and patterns of use of psychotherapeutic drugs: Results from a 1979 national survey of American adults, In Tognoni G, Bellantuono C, Lader M (Eds): Epidemiological Impact of Psychotropic Drugs. Amsterdam, Elsevier, 1981, pp 117-135

5. McGlynn TJ, Metcalf HL (Eds): Diagnosis and Treatment of Anxiety Disorders: A Physician's Handbook. Washington, DC, American Psychiatric Press, 1989

6. DuPont RL: Phobias and Panic—A Physician's Guide to Modern Treatments. Rockville, Md, The Phobia Society of America, 1986

7. Pecknold JC, Swinson RP, Kuch K, et al: Alprazolam in panic disorder and agoraphobia: Results from a multicenter trial—III. Discontinuation effects. Arch Gen Psychiatry 1988; 45:429-436

8. DuPont RL: A Patient's Guide to Getting Off a Benzodiazepine. Rockville, Md, DuPont Associates, 1989

9. DuPont RL, Pecknold JC: Symptoms After Stopping Alprazolam: Relapse or Withdrawal? Presented to the American Psychiatric Association, Dallas, May 1985

10. Ravi NV, Maany I, Burke WM, et al: Detoxification with phenobarbital of alprazolam-dependent poly-substance abusers. J Subst Abuse Treat 1990; 7:55-58

11. Herman JB, Rosenbaum JF, Brotman AW: The alprazolam to clonazepam switch for the treatment of panic disorder. J Clin Psychopharmacol 1987; 7:175-178

12. Smith DE, Wesson DR: Benzodiazepine dependency syndromes. J Psychoactive Drugs 1983; 15:85-95

13. Ornish SA, Zisook S, McAdams LA: Effects of transdermal clonidine treatment on withdrawal symptoms association with smoking cessation—A randomized, controlled trial. Arch Intern Med 1988; 148:2027-2031

14. Weekes C: Hope and Help for Your Nerves. New York, Hawthorne Books, 1969

15. Weekes C: Peace From Nervous Suffering. New York, Hawthorne Books, 1972

16. Weekes C: Simple, Effective Treatment of Agoraphobia. New York, Hawthorne Books, 1976

17. Weeks C: More Help for Your Nerves. New York, Bantam Books, 1987

# Alprazolam Use and Dependence

## A Retrospective Analysis of 30 Cases of Withdrawal

BILL DICKINSON, DO, *Seattle;* PETER A. RUSH, PharmD; *and* ANTHONY B. RADCLIFFE, MD, *Fontana, California*

*From 1986 to 1989, the Chemical Dependency Recovery Program at Kaiser Permanente Hospital, Fontana, California, admitted an increasing number of patients for alprazolam dependence. Severe withdrawal reactions and adverse consequences with use were reported in the literature. In this review of 30 cases of alprazolam dependence and subsequent withdrawal, there was a statistically significant increase in the number of patient hospital days, the subjective symptoms, and staff time spent with patients compared with those in alcoholic controls. Most patients with diagnosed alprazolam dependence used doses in the range recommended by the package information at the time of admission. Patients with low preadmission doses of 1 mg or less per day showed notable withdrawal symptoms. The average duration of use was 29.9 months, considerably longer than suggested effective ranges. Most patients (28) had a chemical dependence history before being placed on alprazolam therapy; 24 had a positive family history of chemical dependence; and 24 had previous or current psychiatric care.*

(Dickinson B, Rush PA, Radcliffe AB: Alprazolam use and dependence—A retrospective analysis of 30 cases of withdrawal, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:604-608)

There is increased debate in the literature regarding the appropriate use of benzodiazepines.[1-4] Humans have been using hypnotic-sedative agents for many centuries, the first recorded use of alcohol being documented in Genesis 9. Barbiturates appeared in the 1930s, and the first benzodiazepines were marketed in the early 1960s. Associated with the use of benzodiazepines have been abuse, dependence, and withdrawal sequelae.[5-8]

For the purpose of this review, "abuse" is defined as the use of mind-altering drugs that cause interpersonal, family, job, legal, financial, or health problems in a person's life. "Dependence" is dysfunction (psychological and sometimes physical) resulting from the interaction between human beings and mind-altering drugs characterized by behavioral and other responses that always include a compulsion to take the drug to experience its psychological effects or to avoid the discomfort of its absence. "Addiction" is a state of periodic or chronic intoxication detrimental to persons and society produced by repeated consumption of a drug. Addiction is marked by a compulsion to use, tolerance, and withdrawal signs and symptoms with abstinence.

Reports of abuse, dependence, and addiction to benzodiazepines have periodically sparked debate in an attempt to reach a consensus on the appropriate use of these drugs. The focus of debate is on setting guidelines for prescribing indications, alternative medications, or therapy instead of benzodiazepines; specific time limits for benzodiazepine use; and reevaluation periods that may include being off all medication or changes in medication.[1-4,7-11] Since the early 1960s when chlordiazepoxide was first introduced, many benzodiazepines have been developed and more are in the process. With new agents there is hope that one day there will be a benzodiazepine that does not lead to dependence. To date, this has not been seen. In addition there is evidence that patients with a previous chemical dependence history, especially to other hypnotic-sedative drugs, are at an increased risk for dependence to develop with the use of benzodiazepines.[7-10,12]

In 1981 the Upjohn Company began marketing alprazolam (Xanax). The primary indication for its use was anxiety.[13] As of 1988, alprazolam was the number one selling benzodiazepine ("Upjohn: Bringing Attention to Anxiety in Children," *Medical Advertising News,* October 15, 1988, pp 8, 26). Its use is being suggested with an increasing array of indications in addition to anxiety (*Diagnostic and Statistical Manual of Mental Disorders,* 3rd edition, revised [DSM-IIIR] codes 300.00, 300.02).[5] Other uses include panic disorder (DSM-IIIR codes 300.01, 300.21),[14] agoraphobia (code 300.22),[14] social phobia (code 300.23),[15] adverse schizophrenic symptoms,[16] and the premenstrual syndrome.[17] Alprazolam is being suggested for treating separation anxiety and generalized anxiety in adolescents. The product circular indicates few side effects as long as dose limits are followed and that dosage reduction should be at a rate of 0.5 mg every three days. In addition, the product circular advises that alprazolam use is not usually indicated for the relief of anxiety or tension associated with the stress of everyday life; effectiveness longer than four months has not been established; and it should not be used in pregnancy or with alcohol.[13] Previous studies of this drug have also indicated low rates of side effects.[14]

The number of reports of problems with alprazolam

From the Careunit, Ballard Community Hospital, Seattle (Dr Dickinson); and the Chemical Dependency Recovery Program, Kaiser Permanente Hospital, Fontana, California (Drs Rush and Radcliffe).

Reprint requests to Peter A. Rush, PharmD, Pharmacist Specialist, Kaiser Permanente Chemical Dependency Recovery Program, 17046 Marygold Ave, Fontana, CA 92335.

during both treatment and withdrawal is increasing. Hostility,[18,19] rebound insomnia,[20] major depression,[21] amnesia, aggressive and violent behavior, mania, hepatitis, hepatomegaly, jaundice, and altered liver function have all been reported during treatment.[14] Severe withdrawal symptoms reported have included seizures,[22-25] rebound anxiety greater than before being placed on alprazolam therapy,[22,26,27] delirium,[24,28] psychosis,[22] mania,[29] paranoia,[29] and increased panic attacks compared with pretreatment levels.[30] Increased cortisol levels have also been seen.[26] Many cases involving generalized benzodiazepine withdrawal symptoms have been reported.[22,24,26,27,31-35] Several reports indicate that standard withdrawal measures, especially substituting other benzodiazepines for alprazolam, have not been effective in treating alprazolam withdrawal.[23,28,33,36] It has been theorized that alprazolam and other triazolobenzodiazepines may work at varying sets or subsets of receptor sites other than those of other benzodiazepines.[22,23,28,33,36] This helps to explain incomplete cross tolerance and may provide insight into the causes of more difficult withdrawal in alprazolam patients. Some reports indicate that patients with a previous history of chemical dependence prefer alprazolam over diazepam.[37,38]

During the past year, the staff at our treatment center have noted that patients in withdrawal from alprazolam have a longer detoxification time, more severe withdrawal symptoms, and require more staff time than other patients. These observations seem to correlate with findings in the medical literature.[26,30,34,39] During the period January 1989 to May 1989, there was a greatly increased number of admissions for alprazolam withdrawal. This has also been seen at some treatment centers.[32]

The following report summarizes 30 cases of alprazolam withdrawal seen from October 1986 through May 1989. Cases of alprazolam withdrawal before October 1986 were not included because our computer data base does not list cases specifically for alprazolam before that date.

## Patients and Methods

In this review we retrospectively analyze 30 cases of alprazolam withdrawal in patients who were admitted for detoxification from October 1986 until May 1989. All cases had a discharge diagnosis of alprazolam dependence (DSM-IIIR codes 292.00, 304.10). Treatments used include supportive counseling, group therapy, and continuing medical regimens used before admission for chronic disorders—such as antihypertensive drugs, asthma treatments, and the like. Pentobarbital substitution and gradual withdrawal were frequently used to minimize physical signs and symptoms of benzodiazepine withdrawal (hypertension, tachycardia, and seizures). In this 32-month period, 1,595 patients were admitted to the inpatient unit at the Chemical Dependency Recovery Program, Kaiser Permanente Hospital, Fontana, California. Patients were referred to the recovery program by other services or departments within the health plan. These 30 cases represent 1.9% of all admissions. All medical records were reviewed by one examiner (B.D.). Information was collected on the admission date, age, sex, race, source of initial alprazolam prescribed, the primary indication for alprazolam use when initially prescribed, chemical dependence history before alprazolam use, family history of chemical dependence, psychiatric history, subjective and physical signs of withdrawal, number of detoxification days, initial prescribed dosage of alprazolam, maximum alprazolam dose used in one 24-hour period, alprazolam dose per day being used at the time of admission, and the duration of use.

The severity of withdrawal was estimated in several areas. The number of patient days spent in primary detoxification were counted. The Chemical Dependency Recovery Program uses predominantly inpatient services for detoxification. This is followed by an intensive outpatient program where the patient spends 9 to 12 hours a day in therapy at the recovery program for an additional one to two weeks. Patients are observed medically during this time and may continue to have some minor withdrawal symptoms. No data from this intensive outpatient program are included in this study. Only primarily detoxification days were counted. The number and type of both subjective and physical withdrawal signs and symptoms were recorded. The number of staff entries per day was noted. Both the withdrawal signs and symptoms and the staff entries are recorded in the patient's chart either during routine general patient monitoring of all patients several times each day or when a patient seeks out the staff because of specific complaints. All entries by the staff attempt to accurately reflect both the patients' specific words and the staff's observations and vital signs measurements.

Alprazolam-dependent patients were compared in each of the preceding areas with a control group. The controls came from a stratified random sample of patients admitted for alcohol dependence between October 1986 and July 1989. Control patients were matched to the alprazolam group on the basis of sex, age, and race.

## Results

### *Admission Date*

Three patients were admitted during 1986, nine patients during 1987, nine patients during 1988, and nine patients from January through May 1989. Of the 30 patients, 9 (30%) were admitted during the last five months of the study. As a point of interest but not included in this study, 3 additional patients in alprazolam withdrawal were admitted during June 1989, giving a total of 12 patients admitted for alprazolam withdrawal in the first six months of 1989.

### *Age*

The average age of admission for the alprazolam cases and controls was 43.7 and 44.4 years, respectively. The age range was 20 to 73 years for the alprazolam group and 25 to 67 for controls. For the study group, 26 patients (87%) were between 30 and 59 years of age compared with 24 (80%) for controls. The difference in mean age between the two groups was not statistically significant ($t = -0.26$, $P > .05$).

### *Sex*

In the study group, 22 (73%) patients were female and 8 (27%) were male. This was identical to controls.

### *Race*

Of the 30 patients, 25 (83%) were white, 4 (13%) were hispanic, and 1 (3%) was black. This was identical to controls.

### *Chemical Dependence History*

Of the 30 patients, 28 (93%) had a chemical dependence by history before being started on alprazolam therapy.

*Family History of Chemical Dependence*

Patients had a family history of chemical dependence as reported by 24 patients (80%) in the alprazolam group and 27 (90%) in the alcohol group. The difference was not significant ($\chi^2 = 1.18$, $P > .05$).

*Psychiatric History*

Of the 30 patients, 24 (80%) had a history of psychiatric care either before or during their alprazolam use. Psychiatric care was reported by 8 (27%) of the controls.

*Initial Dosage of Alprazolam*

In all cases where data were available (29/30), alprazolam was prescribed in the therapeutic dose range at initial use. Data were not available in one case regarding the initial dosage prescribed. The initial dosage ranged from 0.25 mg to 4.0 mg per day.

*Maximum Alprazolam Dose Used in a 24-Hour Period*

The range of maximum dosage used was 0.75 mg to 20.0 mg per day. In 24 patients the dosage was 4.0 mg per day or less and therefore in the therapeutic dose range according to the Xanax product circular. Two patients used 5 mg per day, one used 6 mg per day, two used 8 mg per day, and one patient reported using 20 mg per day.

*Alprazolam Dose per Day at Time of Admission*

The range of the alprazolam dosage used at the time of admission was 0.5 mg to 7.0 mg per day; 27 (90%) patients were at 4.0 mg per day or less. These patients were therefore in the therapeutic dose range listed in the product circular. Patients reported trying to cut down on their use of alprazolam before admission: 21 (70%) had a daily dose of less than their maximum dose at the time of admission. In addition, 9 (30%) patients experienced signs and symptoms of withdrawal from using 1.0 mg per day or less.

*Duration of Use*

The average duration of use was 29.9 months with a range of 4 to 84 months. Five patients (17%) used the drug for ten months or less, two (7%) used it for only four months.

*Source of Initial Use*

Of 26 patients, 19 (73%) received alprazolam from a psychiatrist and 7 patients (27%) received alprazolam from a primary care physician. In the remaining four cases, the original source could not be ascertained.

*Primary Indication for Initial Use*

In 26 cases, alprazolam was used for general anxiety, panic attacks, or agoraphobia. In the remaining four cases, the original indication for beginning alprazolam use was unknown.

*Patient Days*

The average number of days for a patient to have withdrawal signs and symptoms from alprazolam was 8.8; the range was 5 to 18 days. Four patients from the study group and three from the control group left against medical advice. Their patient days were not counted in the average. In comparison, patients undergoing withdrawal from alcohol took an average of 5.9 days to go through most of their withdrawal signs and symptoms. The range for alcoholic patients was 4 to 8 days. Thus, alprazolam withdrawal patients took an average of 2.9 days longer to go through the major part of detoxification than the patients undergoing alcohol withdrawal. The difference was statistically significant ($t = 4.70$, $P = .0001$).

*Subjective Symptoms of Withdrawal*

Alprazolam withdrawal patients had an average of 7.6 different types of complaints described per patient. The following is a breakdown of the percentage of alprazolam withdrawal charts containing specific subjective symptoms: anxiety, 70%; headache, 50%; agitation, 47%; tearful, 47%; nausea and vomiting, 40%; feeling shaky, 37%; nervous, 37%; insomnia, 33%; muscle aches, 33%; restlessness, 27%; fatigue, 27%; mood swings, 27%; anger, 23%; pacing, 20%; fear, 20%; stomach cramps, 20%; isolation, 17%; dizziness, 17%; and panic, 10%. Subjective complaints were not compared against those of control subjects.

*Physical Signs of Withdrawal*

In all, 28 (93%) of the 30 alprazolam patients and 21 (70%) of the 30 alcoholic patients had physical signs of withdrawal. The difference in proportions was statistically significant ($\chi^2 = 5.46$, $P = .02$). In the alprazolam group, these included elevated systolic and diastolic blood pressures, 20; tachycardia, 20; tremors, 15 (50%); and sweating, 1 (3%).

*Staff Entries per Day*

As an assessment of staff time used during withdrawal, the number of staff charting entries per day was measured for each patient. Alprazolam patients had an average of 8.5 staff entries per day with a range of 5.2 to 17.4. Alcoholic patients averaged 7.3 entries per day with a range of 4.3 to 9.8. Alprazolam patients averaged 1.2 more staff entries per day compared with alcoholic patients, the difference being statistically significant ($t = 2.48$, $P = .02$).

## Discussion

There was a pronounced increase in the number of admissions to the Kaiser Chemical Dependency Recovery Program for alprazolam withdrawal in the period from October 1986 through May 1989. This correlates with other studies.[32]

In all, 27 of our patients (90%) admitted for alprazolam withdrawal reported increasing their use of alprazolam over time. This has been seen in previous studies.[39] Of the patients who were admitted, 21 (70%) had tried to cut down on their alprazolam use before admission but were only able to do so slightly. Patients often told the staff at the recovery program that they were unable to reduce their use of alprazolam further, and this was one reason they were convinced of their dependence on the drug. An interesting finding in this review was that 24 patients (80%) were taking alprazolam at dosages within the listed therapeutic dose range at the time of their maximal use and 27 patients (90%) admitted for alprazolam withdrawal were taking alprazolam in a dosage suggested in the package literature at the time of admission. A dependence on low or therapeutic doses of benzodiazepines and an associated low-dose withdrawal syndrome has been described previously in the medical literature.[1,6] This review correlates with those previous findings, suggesting that more caution should be used when prescribing alprazolam because dependence may develop at recommended therapeutic levels. As

reported by Ayd, Rashid and co-workers have recommended that the maximum dose for a 24-hour period should be 1 mg or less.[39] Even at this level, 9 patients (30%) in this study had significant withdrawal signs and symptoms.

The product insert for alprazolam states that "the effectiveness of Xanax for long-term use, that is, more than four months, has not been established by systematic clinical trials." In this study, the average duration of use of 29.9 months greatly exceeded the demonstrated efficacious time listed in the product circular. Considering that 90% of the patients with alprazolam withdrawal were within the suggested dosage range at the time of admission, it is reasonable to suspect that an extended duration of use also contributes to the development of alprazolam dependence. Similar information has already been published for other benzodiazepines.[1,3,6,7,11] Ayd reported that Rashid and associates clearly state that four months should be the maximum length of time for alprazolam use.[39] Other studies have echoed this caution.[1,3,4,7,8,11] In one published report alprazolam withdrawal was described after only eight weeks of use.[35]

Withdrawal from alprazolam has been described as a tedious process[3,34] and unresponsive to standard medical withdrawal regimens.[23,28,33,34,36] Although the product circular recommends reducing the dose of alprazolam at a rate of 0.5 mg every three days, there is little if any support for this procedure in the literature. Most studies have recommended a much slower rate.[3,26,34] One recommended an outpatient reduction of no more than 0.25 mg every two weeks.[3] The information in this study confirms previous reports of severe withdrawal signs and symptoms from alprazolam. Patient days in withdrawal, the number and type of physical signs of withdrawal, and the amount of staff time needed for each patient with alprazolam withdrawal were all notably increased over those in patients with alcohol withdrawal.

Although the medical literature describes seizures occurring in a significant percentage of alprazolam withdrawal patients,[22-25] we found no seizures during the treatment of withdrawal.

## Conclusion

Many studies have concluded that patients with a history of chemical dependence are at an increased risk to become dependent on benzodiazepines.[7-10,12,37,38] One study showed that alprazolam produced more euphoria and drug-induced behavioral changes in alcoholics than in nonalcoholics.[37] Another study found that patients who had a history of benzodiazepine dependence liked to use and sought to use alprazolam instead of diazepam.[38] In light of this, our case reviews found that 28 of 30 patients (93%) with alprazolam withdrawal admitted to the Chemical Dependency Recovery Program had a history of chemical dependence. This history was not always known by the physicians who initially prescribed the alprazolam, and this finding reinforces the need to be extremely cautious in prescribing this drug to patients with such a history. Ciraulo and colleagues have shown evidence that parental alcoholism is a risk in benzodiazepine abuse.[40] We found that 24 of these patients (80%) had a family history of chemical dependence, which supports their conclusion. A family history for dependence should also be obtained and considered before prescribing alprazolam. In addition, we found that 80% of patients (24) admitted for alprazolam withdrawal had a previous or concurrent history of psychiatric illness. This correlates with the finding in this review that a psychiatrist was the source of the initial use of alprazolam in 22 patients (73%) admitted for alprazolam withdrawal. It is known that patients with chemical dependence issues often have a concurrent psychiatric diagnosis. Many of these are related to the dependence or abuse of drugs and alcohol. Both anxiety and panic can accompany use and withdrawal from a variety of substances.

We found that in 100% of the cases, the primary indication for alprazolam use was generalized anxiety, panic attacks, or both. It would therefore seem important to obtain a chemical dependence history and a family history for chemical dependence in any patient under psychiatric care. This will help facilitate the appropriate use of alprazolam, especially to use caution in prescribing for patients with this type of history.

### REFERENCES


1. Woods JH, Katz JL, Winger G, et al: Use and abuse of benzodiazepines. JAMA 1988; 260:3476-3480

2. Lin S, Morse RM, Finlayson RE, et al: Abuse of benzodiazepines. JAMA 1989; 261:2956-2957

3. Bystritsky A: Benzodiazepine withdrawal. South Calif Psychiatr Soc Newslett 1989; 37:10

4. Yates WR, Wesner RB: Advances in anxiety management. J Am Board Fam Pract 1989; 2:38-42

5. Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed Revised. Washington, DC, American Psychiatric Association, 1987

6. Smith DE, Wesson DR: Benzodiazepine dependency syndromes. J Psychoactive Drugs 1983; 15:85-95

7. WHO Review Group: Use and abuse of benzodiazepines. Bull WHO 1983; 61:551-562

8. Dietch J: The nature and extent of benzodiazepine abuse: An overview of recent literature. Hosp Community Psychiatry 1983; 34:1139-1145

9. Ciraulo DA, Sands BF, Shader RI: Critical review of liability for benzodiazepine abuse among alcoholics. Am J Psychiatry 1988; 145:1501-1506

10. Schuckit MA, Morrissey ER: Drug abuse among alcoholic women. Am J Psychiatry 1979; 136(4B):607-611

11. Chiefs of Psychiatry: Guidelines for the Treatment of Insomnia, Anxiety and Panic Disorders in the Primary Care Setting. Pasadena, Calif, Southern California Permanente Medical Group Publication, March 1989

12. Ayd FJ: The abuse liability of alprazolam. Int Drug Ther Newslett 1989; 24:4

13. Product Insert, Xanax. Kalamazoo, Mich, Upjohn Company, 1985

14. Noyes R Jr, DuPont RL Jr, Pecknold JC, et al: Alprazolam in panic disorder and agoraphobia: Results from a multicenter trial. Arch Gen Psychiatry 1988; 45:423-428

15. Reich J, Yates W: A pilot study of treatment of social phobia with alprazolam. Am J Psychiatry 1988; 145:590-594

16. Csernansky JG, Riney SJ, Lombrozo L, et al: Double-blind comparison of alprazolam, diazepam, and placebo for the treatment of negative schizophrenic symptoms. Arch Gen Psychiatry 1988; 45:655-659

17. Smith S, Rinehart JS, Ruddock VE, et al: Treatment of premenstrual syndrome with alprazolam. Obstet Gynecol 1987; 70:37-43

18. Rosenbaum JF, Wood SW, Groves JE, et al: Emergence of hostility during alprazolam treatment. Am J Psychiatry 1984; 141:792-793

19. Rapaport M, Braff DL: Alprazolam and hostility (Letter). Am J Psychiatry 1985; 142:146

20. Kales A, Bixler EO, Vela-Bueno A, et al: Alprazolam: Effects on sleep and withdrawal phenomena. J Clin Pharmacol 1987; 27:508-515

21. Lydiard RB, Laraia MT, Ballenger JC, et al: Emergence of depressive symptoms in patients receiving alprazolam for panic disorder. Am J Psychiatry 1987; 144:664-665

22. Browne JL, Hauge KJ: A review of alprazolam withdrawal. Drug Intell Clin Pharm 1986; 20:837-841

23. Kantor SJ: A difficult alprazolam withdrawal. J Clin Psychopharmacol 1986; 6:124-125

24. Levy AB: Delirium and seizures due to abrupt alprazolam withdrawal. J Clin Psychiatry 1984; 45:38-39

25. Breier A, Charney DS, Nelson JC: Seizures induced by abrupt discontinuation of alprazolam. Am J Psychiatry 1984; 141:1606-1607

26. Mellman TA, Uhde TW: Withdrawal syndrome with gradual tapering of alprazolam. Am J Psychiatry 1986; 143:1464-1466

27. Vital-Herne J, Brenner R, Lesser M: Another case of alprazolam withdrawal syndrome (Letter). Am J Psychiatry 1985; 142:1515

28. Zipursky RB, Baker RW, Zimmer B: Alprazolam withdrawal delirium unresponsive to diazepam. J Clin Psychiatry 1985; 46:344-345

29. Bleich A, Grinspoon A, Garb R: Paranoid reaction following alprazolam withdrawal. Psychosomatics 1987; 28:599-600

30. Fyer AJ, Leibowitz MR, Gorman JM, et al: Discontinuation of alprazolam treatment in panic patients. Am J Psychiatry 1987; 144:303-308

31. Patterson JF: Alprazolam dependency—Use of clonazepam for withdrawal. South Med J 1988; 81:830-836

32. Juergens SM, Morse RM: Alprazolam dependence in seven patients. Am J Psychiatry 1988; 145:625-627

33. Alprazolam withdrawal. Mass Gen Hosp Newslett Biol Ther Psychiatry 1987; 10:11

34. Ayd FJ: Alprazolam withdrawal. Int Drug Ther Newslett 1986; 21:28

35. Noyes R, Clancy J, Coryell WH, et al: A withdrawal syndrome after abrupt discontinuation of alprazolam. Am J Psychiatry 1985; 142:114-116

36. Votolato NA, Batcha KJ, Olson SC: Alprazolam withdrawal (Letter). Drug Intell Clin Pharm 1987; 21:754-755

37. Ciraulo DA, Barnhill JG, Greenblatt DJ, et al: Abuse liability and clinical pharmacokinetics of alprazolam in alcoholic men. J Clin Psychiatry 1988; 49:333-337

38. Schmauss C, Apelt S, Emrich HM: The seeking and liking potentials of alprazolam (Letter). Am J Psychiatry 1988; 145:128

39. Ayd FJ: Problems associated with alprazolam therapy. Int Drug Ther Newslett 1988; 23:29-31

40. Ciraulo DA, Barnhill JG, Ciraulo AM, et al: Parental alcoholism as a risk factor in benzodiazepine abuse: A pilot study. Am J Psychiatry 1989; 146:1333-1335

**Addiction Medicine**
**and the Primary Care Physician**

# Abuse of Prescription Drugs

BONNIE B. WILFORD, *Chicago*

*An estimated 3% of the United States population deliberately misuse or abuse psychoactive medications, with severe consequences. According to the National Institute on Drug Abuse, more than half of patients who sought treatment or died of drug-related medical problems in 1989 were abusing prescription drugs. Physicians who contribute to this problem have been described by the American Medical Association as dishonest—willfully misprescribing for purposes of abuse, usually for profit; disabled by personal problems with drugs or alcohol; dated in their knowledge of current pharmacology or therapeutics; or deceived by various patient-initiated fraudulent approaches. Even physicians who do not meet any of these descriptions must guard against contributing to prescription drug abuse through injudicious prescribing, inadequate safeguarding of prescription forms or drug supplies, or acquiescing to the demands or ruses used to obtain drugs for other than medical purposes.*

(Wilford BB: Abuse of prescription drugs, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:609-612)

The use of drugs in America is strongly influenced by the social, economic, political, and scientific and technologic environments that define our society. In fact, we are a drug-taking society whose general outlook is that every malady has a treatment and that this solution lies mainly in the use of medicinal agents. We have a social and cultural expectation that there is a "pill for every ill." Medications have come to play such an important role in the interchange between physicians and patients that often the prescription is viewed as an expected medium of exchange between patient and prescriber. A prescriber has not concluded his or her application of skills until a prescription has been written for the cure. The closure of a visit between patient and physician is symbolized by the prescription being handed to the patient.[1]

Recognizing patients who misuse such medications or who seek psychoactive drugs for the purpose of intoxication or resale to others constitutes a clinical problem for which medical school preparation is lacking. Yet the number of such patients is large—3% of the population, according to federal estimates[2]—and the consequences of such use severe. In surveys by the National Institute on Drug Abuse, more than half of patients who sought treatment for or died of drug-related medical problems were abusing prescription drugs.[3]

From the perspective of the health care system and clinicians, there are three variants of prescription drug abuse:

- Patients who present with an established dependence on a prescription drug;
- Those in whom iatrogenic drug dependence develops as the result of injudicious prescription practices or the use of multiple physicians, or both, or self-medication rather than compliance with a physician's directions; and
- Patients who seek drugs to divert them—that is, to acquire drugs to sell.

Despite these differences in motive, the drug-seeking behavior itself has many similarities.

The Council on Scientific Affairs of the American Medical Association clearly defined the sources of prescription drug abuse in its 1981 report, "Drug Abuse Related to Prescribing Practices."[4] In that report, the Council described as contributing to the problem those practitioners who engage in willful and conscious misprescribing for the purposes of drug abuse, usually for profit; accede to inappropriate demands for medications by patients; prescribe in an uninformed way because they have not kept pace with developments in drug therapy; or whose professional judgment is impaired by virtue of personal problems with drugs or alcohol. The Council also identified patient manipulation of prescription orders—by theft, alteration, or forgery—and theft of drugs as major elements of concern.

Having defined the dimensions of the problem, the Council called on physicians to guard against contributing to prescription drug abuse through injudicious prescribing practices or by acquiescing to the demands of certain patients for instant chemical solutions to all their problems. Each physician should convey to patients the concept that all drugs—no matter how helpful—are only part of an overall plan of treatment and management.

Even when sound medical indications have been established for using a psychoactive drug, three additional factors should be considered in deciding on the dosage and duration of drug therapy[5]:

- The severity of symptoms, in terms of a patient's ability to accommodate them. Relief of symptoms is a legitimate goal of medical practice, but using many psychoactive drugs to achieve complete symptomatic relief requires caution because of the abuse potential and dependence liability of these drugs.

From the Department of Substance Abuse, American Medical Association, Chicago.
Reprint requests to Bonnie B. Wilford, Director, Department of Substance Abuse, American Medical Association, 535 N Dearborn St, Chicago, IL 60610.

• A patient's reliability in taking medication, noted through observation and careful history-taking. A physician should assess a patient's susceptibility to drug abuse before prescribing any psychoactive drug and weigh the benefits against the risks. The possible development of dependence in patients on long-term therapy should be monitored through periodic check-ups and family consultations.

• The dependence-producing capability of the drug. Patients should be warned about possible adverse effects caused by interactions with other drugs, including alcohol.

## Compliance

The question of a patient's compliance with a prescribed drug regimen becomes especially pertinent when the drug in question has potential for abuse. Surveys of patient compliance are not reassuring; as many as half of all patients sampled have deviated from the physician's directions by never obtaining a prescribed drug; never taking the prescribed drug; taking the prescribed drug improperly, which involves taking an incorrect quantity per dose or an incorrect number of doses per day, omitting or "doubling up" doses, or discontinuing the drug prematurely; or taking nonprescribed drugs or discontinued medications in addition to or in place of the prescribed drug.[5] The use of alcohol is frequently mentioned in this last category.

Patient compliance is enhanced if the flow of information between physician and patient is open and reciprocal. Especially in prescribing psychoactive medication, a physician should carefully describe the purpose and use of the drug, as well as important adverse effects that might be experienced.

In situations where a patient's motives are not clear and a history or physical examination indicates that the complaint may be real, the physician should prescribe the smallest possible amount of an appropriate drug pending the results of confirming diagnostic procedures.[6]

## Identifying 'Conning' in a Patient

Aside from patients who fail to comply with a prescribed drug regimen through lack of information or insufficient motivation, prescription drug misuse has another face—long-term drug abusers who approach physicians for the specific purpose of securing drugs to support their dependence. In the drug culture, such an approach is known as "working" or "making a doctor." Almost every physician will encounter these "conning" patients, whether in private practice, a clinic setting, a neighborhood health center, a busy emergency department, a rural area, or a large metropolitan hospital. Manipulative approaches used by such patients are outlined in Table 1.[7,8]

### *Feigning Physical Problems*

A variety of physical problems can be convincingly portrayed by drug-seeking patients. These run the gamut from bleeding—often stimulated by the use of anticoagulants—and self-inflicted skin lesions, to gastrointestinal and musculoskeletal disorders. Three of the most common presenting ailments among patients seeking narcotic drugs are renal colic, toothache, and tic douloureux.

A patient feigning renal colic complains of pain on the left side of the body (to avoid a diagnosis of appendicitis) and a burning sensation on urination. If the physician asks for a urine specimen, the patient might even prick his or her finger and drop a little blood into the urine.

TABLE 1.—*Disorders Feigned by Drug Seekers*

| | |
|---|---|
| Migraine headaches | Sickle cell crisis |
| Tic douloureux | Metastatic cancer |
| Back pain | Bronchitis |
| Colitis | Psychiatric disorders |
| Renal colic | Attention deficit syndrome |
| Acute or chronic pain from orthopedic injury | Narcolepsy |
| Toothache | Concern over obesity |

Patients presenting with toothache often claim to be from another town and to have left at home the medications prescribed by their dentist. Should the physician wish to verify this claim, the telephone number supplied for the hometown dentist often is that of an accomplice. If the person actually has an abscessed tooth, he or she usually makes full use of it by visiting a series of physicians and dentists to ask for pain medication.

Tic douloureux is a favorite approach among patient "hustlers" because it has no clinical or pathologic signs. Patients complain of recurring, intense episodes of facial pain lasting several seconds to several minutes. Some patients are able to contort their faces to simulate an attack of pain.

### *Feigning Psychological Problems*

Most drug seekers who feign psychological problems are attempting to obtain stimulants or depressants rather than analgesics. The psychological symptoms most often presented include anxiety, insomnia, fatigue, and depression.

### *Deception*

Manipulative techniques used to deceive physicians include prescription theft, forgery, and alterations, concealing or pretending to take medications, and requesting refills in a shorter period of time than originally prescribed—often with the excuse that the medication was lost or stolen.

### *Pressuring the Physician*

Coercive tactics include eliciting sympathy or guilt, such as by suggesting that medical treatment caused the patient's drug dependence, direct threats of physical or financial harm, the offer of bribes, or using the names of family members or friends.

### *Forging Prescriptions*

Prescriptions are forged in one of the following ways[9]:

*Altering a prescription written by a physician.* Figure 1 shows three prescriptions, before and after forgery. In each case, the drug seeker used a pen with the same color ink. In the first example, the dispensing number, written only in arabic numberals, is easily altered by the forger. The second example shows that, contrary to popular belief, dispensing numbers written in longhand also can be changed. Some drug seekers alter the number of refills on the prescription.

*Forging prescriptions from scratch.* The forger begins with either a blank piece of paper or a legitimate prescription blank from a practicing physician. In the former case, the forger stencils a physician's name and address (as well as the telephone number of an accomplice) in black lettering onto a blank page and then uses a photocopier to reduce the sheet to the usual size of a prescription. Because the Drug Enforce-

ment Agency registration is now valid for three years, drug seekers are always on the lookout for the names of physicians who have retired, left the state, or died. Some drug seekers use desktop publishing to produce clever forgeries using such assumed identities.

To a drug seeker, a blank prescription is like a blank check. Prescription blanks are frequently stolen from emergency departments and clinics, in part because of the carelessness of the medical staff. The Missouri Task Force on the Misuse, Abuse and Diversion of Prescription Drugs has published the following guidelines for the care and use of prescription blanks[10(pp2-3)]:

- Store all unused prescription pads in a safe place;
- Limit the number of pads in use at one time;
- Number prescription blanks so that missing blanks may be detected easily;
- Never sign prescription blanks in advance;
- Write prescriptions in ink or indelible pencil;
- Use a combination of longhand, plus arabic and roman numerals, to indicate the amount of drug precribed; and
- Do not use prescription blanks for instructions to patients or memos.

Although many "conning" tactics seem obvious when described, they can be used convincingly, especially in the midst of a busy medical office or emergency department. Physicians can protect themselves, however, if they are alert to certain behaviors that are common among drug seekers.[3,5,8]

### *The Transient Patient*

Frequently a patient is from out of town and has lost or had his or her medication stolen. The patient tries to create a sense of urgency and pressures the physician for an immediate response by claiming intense pain. Frequently ordinary clinical intuition will alert the physician that there is a large discrepancy between the patient's report of the severity of the pain and the level of pain actually being experienced.

Some patients' manipulativeness can be detected by observation. For example, when a physician has the impression that his or her responses are being studied by the patient as intensely as the physician is studying the patient's situation, the physician should be suspicious that a "doctor shopper" or "conning" patient is at hand. The ordinary patient does not scan the physician for responses in the same way in which those trying to "con" may. This difference is detectable if a physician maintains a reasonable level of awareness.

### *The 'Spell-Binding' Patient*

Patients with pseudologica fantastica or Munchhausen's syndrome, or those who are adept at deceit, can be persuasive to a degree that is unusual in comparison to ordinary clinical encounters. When the physician has the feeling that the patient has extraordinary persuasive and dramatic powers, suspicion that a manipulator may be present is justified.

The patient who has no interest in diagnosis, fails to keep appointments for x-ray films or laboratory tests, or refuses to see another physician for consultation should be suspected. Most manipulative patients shun real workups and resist attempts to verify history, whereas genuine patients rarely refuse such efforts.

The pressure drug seekers can bring to bear on a physician are considerable. A physician who is alert to the tactics employed by these persons usually can avoid being deceived or manipulated, however. When a patient uses such tactics, the physician should maintain control of the physician-patient relationship, remain professional despite the ploys for sympathy or guilt, and regard the drug seeker as a patient with a serious illness.[3,4]

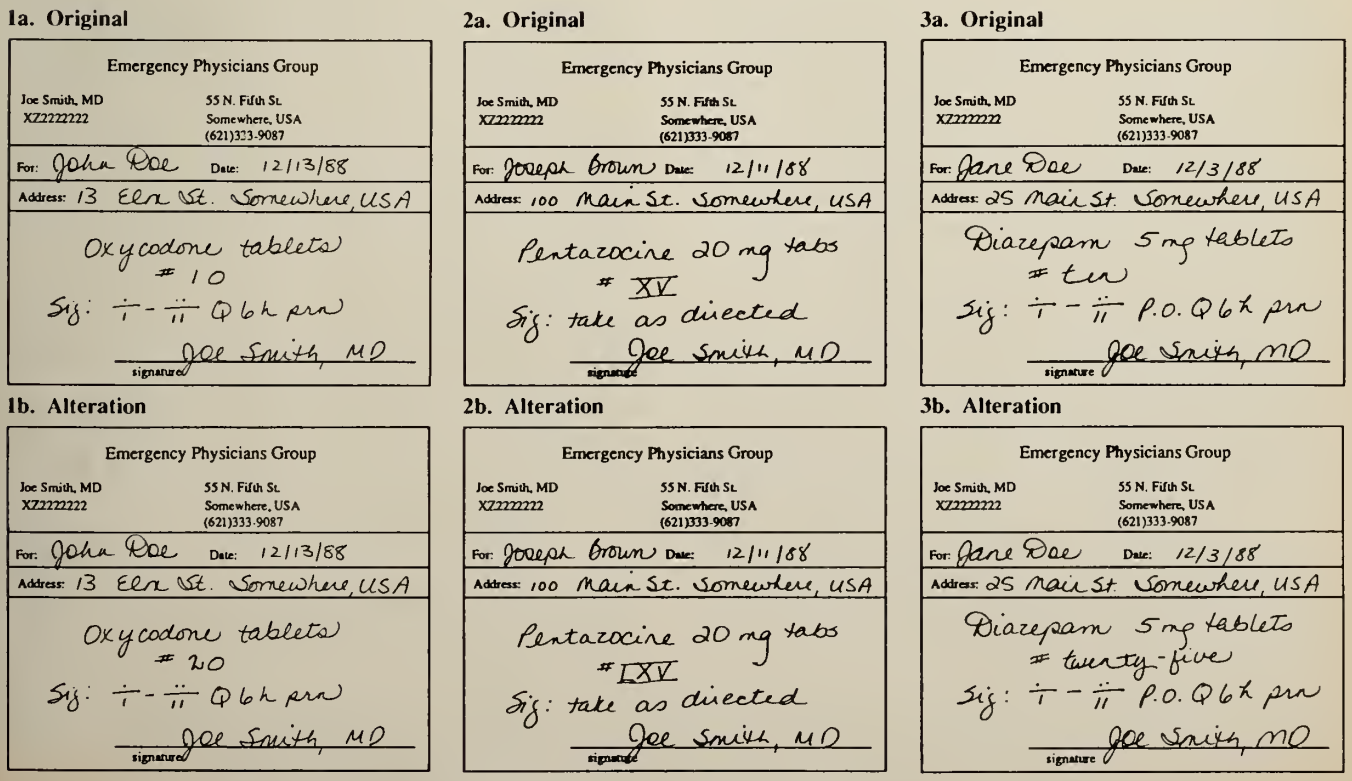



**FIGURE 1.**—Three typical prescriptions are shown before and after being forged (from Goldman[9]).

## Confronting the Drug Seeker

It is usually difficult to prove that a patient is a drug seeker from the information obtained during a single visit. Although most of the time the diagnosis is at best a guess, a physician may find the following strategies useful when confronting suspected drug seekers:

- Always give advice with reference to the patient's chief complaint. For example, physicians who do not ordinarily prescribe narcotic-containing cough syrups for bronchitis should say so to the patient.
- Maintain a professional demeanor throughout the encounter. Drug seekers who are frustrated in their attempts to obtain drugs often become angry. This response is so typical that some clinicians consider it diagnostic of drug-seeking behavior. Frustrated drug seekers may shout obscenities at the staff; others threaten violence, but such threats are seldom carried out. If necessary, security staff or the police should be summoned.
- Confront the patient in a gentle, respectful manner. It is important to avoid being judgmental or showing antagonism. A variety of confrontation techniques may be used. Some examples are inquiring as to whether the patient believes that he or she has a problem with prescription drugs, noting the addictive properties of the medications sought, and expressing concern for the patient's welfare. When confronted, some patients admit that they are addicted to prescription drugs and claim that they want to stop taking them. These patients should be referred for formal assessment and treatment.

A dilemma commonly encountered is whether to provide a patient with a supply of drugs until he or she can obtain treatment for the underlying dependence. What to do depends in part on which prescription drugs the patient abuses. Withdrawal from narcotics can be debilitating, but it is rarely fatal. Withdrawal from barbiturates or benzodiazepines, on the other hand, can be fatal, and patients addicted to these drugs should be held in a medically supervised setting for management of withdrawal. In addition, there are important legal issues to be considered.[2]

Another dilemma for a physician is whether to believe drug seekers' claims that they wish to stop their drug use. The admission itself may be genuine, but it also may be another ruse. When in doubt, patients should be referred to a specialist in drug rehabilitation for expert consultation.

In all cases, patients should be given the benefit of the doubt. It is important to remember that even drug seekers may present with illness not related to their drug addiction and that addiction is a chronic, relapsing disease.

### REFERENCES

1. Manasse HR: Medication use in an imperfect world: Drug misadventuring as an issue of public policy, part 2. Am J Hosp Pharm 1989; 46:1141-1152

2. Drug Enforcement Administration: Guidelines for Prescribers of Controlled Substances. Washington, DC, US Dept of Justice, 1987

3. Wilford BB: Prescribing Controlled Drugs. Chicago, American Medical Association, 1987

4. Proceedings of the House of Delegates 269. Chicago, American Medical Association, 1971

5. Cohen S: Drug abuse and the prescribing physician, *In* Buchwald C, Cohen S, Katz D, et al (Eds): Frequently Prescribed and Abused Drugs: Their Indications, Efficacy and Rational Prescribing. Natl Inst Drug Abuse Monogr Ser 1980; 2:1-6

6. AMA Department of Drugs: AMA Drug Evaluations, 5th Ed. Chicago, American Medical Association, 1983, pp 5-10

7. Chappel JN: Patient Manipulation of the Physician. Workshop on the Ethics and Practice of Prescribing Psychoactive Drugs. San Francisco, Haight Ashbury Training and Education Project, 1980

8. Wilson SJ, Gilmore R: Manipulative tactics of narcotics addicts. Med Times 1974; 102:81-84

9. Goldman G: Frustrating prescription drug seekers. Emerg Med Rep 1988; 9:26-32

10. Physician Handbook. Jefferson City, Mo, Missouri Task Force on the Misuse, Abuse and Diversion of Prescription Drugs, 1988

**Addiction Medicine**
**and the Primary Care Physician**

# Prescription Drug Abuse

## Patient, Physician, and Cultural Responsibilities

DONALD R. WESSON, MD, *and* DAVID E. SMITH, MD, *San Francisco*

*The abuse of prescription drugs is one facet of America's drug problem that is particularly complex because access to prescription drugs must be maintained for some purposes and contained for others. The American Medical Association has sponsored two national conferences to grapple with the confluence of the medical access to prescription drugs and a national drug abuse control policy. One result has been a classification of misprescribing physicians that blames physicians for prescription drug abuse. The conceptualization and public policy response to prescription drug abuse have been largely shaped by the emotional response to the epidemic of crack cocaine and other nonprescription drug abuse. A new perspective is needed—one that accommodates the evolving role of physicians in society, the lifestyle choices that physicians enable in their patients, and the respective responsibilities of both physicians and patients in physician-patient transactions.*

(Wesson DR, Smith DE: Prescription drug abuse—Patient, physician, and cultural responsibilities, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:613-616)

In 1980 the American Medical Association (AMA) sponsored a White House Conference on Prescription Drug Abuse that drew attention to the abuse of prescription drugs as one facet of the nation's growing drug problem. In the intervening ten years, the Drug Enforcement Administration, state medical licensing boards, and local drug abuse agencies have expended great efforts to curb prescription drug abuse, and, as shown in Figure 1, many regulatory agencies oversee the manufacture and distribution of prescription psychotropic medications that have abuse potential. Despite triplicate prescriptions, new laws, and an increasing web of regulations designed to control prescription medications, the abuse of prescription drugs has continued.

In December 1988, the AMA's Department of Substance Abuse, headed by Ms Bonnie Wilford, sponsored a second national conference on prescription drug abuse. The conference—which included plenary sessions and workshops covering clinical and epidemiologic aspects of prescription drug abuse and regulatory strategies for curbing prescription drug abuse—brought together speakers from drug law enforcement, organized medicine, medical practice regulatory bodies, and a representative from the Narcolepsy Foundation representing the patients' perspective.

The basic positions of medicine and regulatory agencies have changed little in the years between conferences. The patients' perspective was a superb anchor to discussions of prescription drug abuse in which the legitimate need some patients have for access to the medication is often overlooked.

But the conference was also remarkable by what was missing. There were no discussions of the many underlying assumptions that shape attitudes and ideas about prescription drug abuse. Prescription drug abuse is more difficult to conceptualize than the abuse of cocaine, marijuana, or even alcohol because there is the need for a balance between restricting access and maintaining availability in drug control policy.

### What Is Prescription Drug Abuse?

Prescription drug abuse is a nebulous construct whose common denominator is that medicinals manufactured by the pharmaceutic industry are being used in ways that were not intended by regulatory agencies and in ways that are not approved by the mainstream culture. Lumped together is a range of patient, physician, and addict behaviors. At one end are those physicians who, for personal profit, sell prescriptions to drug addicts who will use the medications to "get high." At the other are patients being treated for a medical condition who take more of a medication than an addiction specialist deems appropriate. Epidemiologists describe occurrences of drug-correlated adversities that appear in emergency departments as prescription drug abuse, clinicians describe cases of addiction to prescribed medication, and enforcement officers speak of physicians who deal drugs—all trying to communicate with one another without a common frame of reference. What is needed to design more effective intervention strategies for prescription drug abuse is a better operational definition of physician, patient, or addict behaviors that relates to prescription drug abuse.

### Why Is Prescription Drug Abuse So Abhorrent?

Participants in both AMA conferences uniformly condemned prescription drug abuse—however they defined it. The common view is that medicinals are intended to treat

From the Departments of Psychiatry (Dr Wesson) and Occupational Medicine (Dr Smith), University of California, San Francisco, School of Medicine; the Department of Psychiatry, Veterans Administration Medical Center, San Francisco (Dr Wesson); the Department of Research, Los Angeles Drug Abuse Treatment Research Center (Dr Wesson); the Research Department, Merritt Peralta Institute, Oakland, California (Drs Wesson and Smith); and the Haight-Ashbury Free Clinics, San Francisco (Dr Smith).

This work was supported in part by grant No. R18-DA6082 from the National Institute on Drug Abuse to the Los Angeles Drug Abuse Treatment Research Center.

Reprint requests to Donald R. Wesson, MD, Merritt Peralta Institute, 435 Hawthorne Ave, Oakland, CA 94609.

disease and that physicians should prescribe medications only to treat disease. Any other use of their medicinals is unethical, criminal, or both.

This definition of physicians' role in society does not reflect the reality of physicians' range of practice. For example, birth control, abortions, and cosmetic surgical reconstructions—accepted medical practices that have to do with enabling personal choices rather than treating illness—involve the prescription of "medications" for purposes other than the treatment of disease. Physicians are uniquely restricted in their prescription of psychotropic medications.

The question is why physicians' prescribing of psychotropic medication for nonmedical purposes is so vehemently abhorred in this culture. Clearly, the prohibition of prescription psychotropic drugs is an extension of the dominant culture's selection of alcohol as the permissible social-psychoactive drug and its prohibition of all other drugs.

Many people now point out that the cultural enabling of alcohol use and the concomitant prohibition of the recreational use of other drugs is determined more by cultural tradition than pharmacology. Without question, the toxicity of many prescription psychotropic drugs does not exceed that of alcohol. Many laypeople and some physicians think that the responsible use of prescription medications for purposes other than the treatment of disease should be permissible and that access through physicians and pharmacies would be preferable to illicit, unregulated, and uncontrolled black-market access.

## Why Is the Physician Blamed?

When a patient abuses a psychoactive medication that a physician has prescribed, it is usually the physician, not the patient, who is held legally and morally responsible. This physician-at-fault theme permeates both medical and legal discussions of prescription drug abuse and was generally echoed by speakers at both AMA-sponsored conferences. The AMA itself has adopted a categorization of physician misprescribers—the dated, the disabled, the dishonest, and the duped (the four "D's")—that assigns fault to physicians. The category-wide assignment of fault by the AMA seems particularly incongruent. An understanding requires a knowledge of how the classification system arose.

The four-D classification—conceived and developed by one of us (D.E.S.)—was first presented at the White House Conference on Prescription Drug Abuse in 1980.[1] Smith and Seymore's intent was to stimulate educational alternatives for the dated or duped physicians, who at that time were either being prosecuted in the same manner as dishonest physicians or were allowed to continue misprescribing because there was no alternative to disciplinary intervention. The four-D classification was pragmatically useful, and several state medical licensing boards subsequently initiated prescribing practice educational alternatives to discipline.

After the White House Conference, Emanuel Steindler, who was on the AMA staff, incorporated the four-D classification into an AMA position paper, which was subsequently adopted as an official stance of the AMA.[2] The AMA took a leadership role in advancing a pluralistic approach to physician misprescribers.

Although Drug Enforcement Administration and other regulatory agencies also adopted the classification, they often perceived an overlap between dishonest physicians and dated or duped physicians and they viewed physicians disabled by personal addiction as "willful misprescribers" who should be prosecuted.

Thus, the classification, which started as an educational

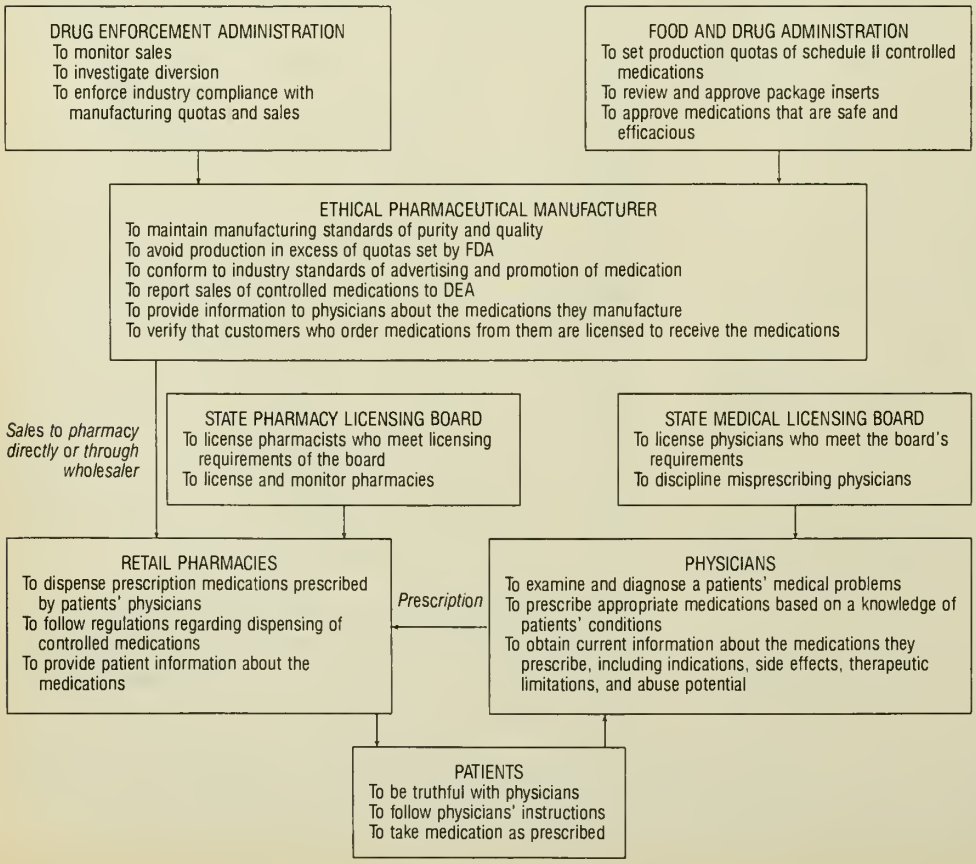



**Figure 1.**—The diagram shows the responsibilities of those involved in the manufacture and distribution of prescription psychotropic medications with abuse potential.

device, has taken on institutional and legal meanings far beyond its original intent. Its association with fault and moral responsibility is entangled in the tradition of medicine and the history of popular antidrug sentiment. Releasing it requires that it be gently disentangled through a realistic understanding of the responsibilities of physicians and patients in a physician-patient relationship and then reframed with antidrug sentiment in the background.

The physician-patient interaction involves respective responsibilities that are part of our culture. The salient responsibilities, summarized in Table 1, are so much a part of our cultural tradition that they are rarely made explicit, and we can generally assume that most physicians and patients know their respective responsibilities. Physicians are responsible for having as their primary concern their patients' well-being and for providing the time, skill, and knowledge to diagnose and treat their patients' disease or condition. Patients are responsible for seeking medical attention for diseases or conditions that they believe a physician can cure or ameliorate, for providing their physicians with the best information possible, and for following their physicians' directions.

The physician-patient relationship is seriously distorted when either party fails to abide by his or her responsibilities. Thus, the breach of responsibility should be the basis for assigning fault.

*Dated Physicians*

Some physicians misprescribe psychoactive drugs because the information on which they base their therapeutic choices is obsolete, incomplete, or wrong. Such physicians have violated their responsibility to their patients by not keeping abreast of current prescribing practices and of abuse patterns of psychoactive drugs. Thus, they cannot meet their responsibility to practice medicine at the same standard as other practitioners in the community.

Prescribing practices change over time as new medications become available or as new clinical information becomes established by scientific study. In the absence of reasonable clinical certainty established by well-conducted clinical trials, prescribing standards for psychotropic medications are established primarily by clinical consensus. The consensus is influenced by many factors, among them societal values, the schedule of the medication, reports of toxicity, and current abuse patterns involving the medication.

The use of amphetamines for weight control is illustrative. The balance has shifted against their use for weight control, not because more efficacious medications have been developed but rather because of the view that their potential for abuse outweighs their therapeutic benefit in controlling weight. Physicians who prescribe amphetamines for weight loss today would be hard-pressed to justify their prescriptions; yet, in the 1950s this was accepted medical practice. Physicians have the responsibility to follow current prescribing practices. Outdated physicians have failed in their responsibility to keep current on prescribing information.

*Disabled Physicians*

Physicians whose judgment is impaired by mental illness or by their own use of psychoactive drugs may prescribe psychotropic medications at variance with accepted practices. A few impaired physicians prescribe excessive amounts of the psychoactive medication or medications that they themselves are taking. More often, however, such physicians may withhold from patients medications that are medically indicated because these physicians fear drawing attention to themselves. In either case, they breach their responsibility to their patients because they do not bring to the physician-patient relationship their best judgment, attention, and skill.

*Dishonest Physicians*

Dishonest physicians are those who use their medical license to deal drugs. When drug addicts consult a dishonest physician, the physician does not have his or her patient's well-being as the primary concern. Such physicians are not treating illness; they are perpetuating addiction while creating the illusion of medical practice to avoid prosecution.

The identification of such physicians pivots on determining their motive. Unfortunately, their motive is not directly observable and must be inferred from their behavior. The motive is obvious when a physician's behavior matches the classic profile of the "script doc"—a physician whose fees

TABLE 1.—*The Responsibilities of Physicians and Patients in the Physician-Patient Interaction*

| *Physician* | *Patient* |
|---|---|
| To have the patient's well-being as his or her primary concern | To seek medical attention for conditions that he or she believes that a physician can cure or ameliorate |
| To formulate a working diagnosis of the patient's problem based on the patient's history and examination | To be truthful in relating historical information and to cooperate with the physical examination |
| To obtain appropriate laboratory tests—or consultations with specialists—to clarify diagnosis | To cooperate in obtaining the laboratory tests—or consultations—requested by the physician |
| To prescribe appropriate therapy (assumes that the physician is acting within his or her scope of expertise and that the physician possesses about the same level of knowledge as other practitioners in the community) | To comply with the physician's instructions, such as taking medications as prescribed and avoiding activities that would complicate or aggravate the disease |
| To monitor the effect of treatment, including monitoring for side effects or toxicity | To report symptoms accurately |
| To continue follow-up until the condition is resolved or the patient's care is assumed by another physician | To follow through with follow-up appointments until discharged by the physician |

TABLE 2.—*The Physician and Patient Contribution in Each of the American Medical Association's Categories of Misprescribing Physicians*

| *AMA Physician Category* | *Physician's Contribution* | *Patient's Contribution* |
|---|---|---|
| Dated | Fails to keep current with prescribing practices or knowledge about current drug abuse patterns | ... |
| Disabled | Fails to exercise optimal judgment because of impairment | ... |
| Dishonest | Subverts medical practice for personal financial gain | Uses physician as drug dealer, not for medical care |
| Duped | Fails to detect deception Allows himself or herself to be manipulated into prescribing at variance with accepted medical practices | Falsifies or withholds information |

are dependent on the quantity and type of drug prescribed. It is less so when a dishonest physician closely simulates in his or her office procedures legitimate medical practice. But the identification of dishonest physicians should not be difficult for ethical physicians. Dishonest physicians fail to meet every physician responsibility.

*Duped Physicians*

A duped physician is one who inadvertently supplies drugs to a drug abuser because the physician has been deceived by a drug abuser posing as a patient. As noted in Table 2, it is primarily the "patient" who has failed to meet his or her responsibility.

Drug abusers who do not want their drug dependence treated but rather want access to the medications for which a physician is the gatekeeper may create the illusion for physicians that they are seeking medical attention for a disease or illness for which the desired drug would be appropriate. Scams for medications can be quite sophisticated, innovative, and impossible to unravel in the time available for the physician-patient interaction.

The term "duped" is not always appropriate in these situations because it implies that a physician is careless, easily deceived, or foolish. It has an implied converse: that careful, competent physicians would not have been duped because they would have recognized the deception. Many who work with such patients have been victims of deception on occasion and suspect that, given the right circumstances, any physician who would undertake the care of such patients could be deceived for a period of time. Why should physicians be at fault when they are the victims of deception?

This question should be of considerable concern to physicians because the issue has been the substance of malpractice suits, disciplinary proceedings, and criminal charges against physicians.

Important dynamics make physicians vulnerable to being held at fault, even when the fault should reasonably rest with the patient. First is the concept of drug addiction as a disease. Many people misunderstand the disease concept and reason that because patients are not at fault for having a disease, they should not be held accountable for their behavior when it is caused by their disease. People who hold this position are understandably reluctant to hold patients at fault. Because someone must be at fault, a physician is blamed. But when patients have used deception to obtain medications or use them in ways other than those prescribed by their physicians, they have violated their responsibility in the physician-patient relationship.

## Conclusion

The efforts of the AMA and the four-D classification of misprescribing physicians have helped state medical licensing boards and enforcement agencies develop ways of intervening with misprescribing physicians sooner and with a broader range of options. The next step is to further refine the application of this system.

Physicians who fail in their responsibilities to patients should be censured, but the current tendency to assign fault to physicians when patients have violated their responsibility is unreasonable and unfair to physicians. When patients are dishonest in the physician-patient relationship and deceive their physicians, or when patients use their medications other than as prescribed, society should hold the patients, not the physicians, accountable for the inevitable adverse consequences.

### REFERENCES

1. Smith DE, Seymore RB: Prescribing practices: The educational alternative for the misprescriber. Proceedings of the White House Conference on Prescription Drug Abuse, Washington, DC, 1980

2. Council on Scientific Affairs: Drug abuse related to prescribing practice. JAMA 1982; 247:864-866

# Diversion Programs for Impaired Physicians

RICHARD IKEDA, MD, MPA, *and* CHET PELTON, *Sacramento, California*

*Nine states have legislated impaired physician programs administered by state medical boards (2), by independent agencies (4), or by medical societies through contracts with medical boards (3). All other state programs are administered by medical societies. California's diversion program has been in effect for more than 10 years. It was the first program for alcohol- and drug-addicted physicians in the country administered by the state agency that also disciplines physicians. Of the physicians who enrolled in this program, 72% have completed it successfully. A total of 618 physicians have been accepted into the program since its inception, with 247 physicians currently participating.*

(Ikeda R, Pelton C: Diversion programs for impaired physicians, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:617-621)

In 1980 the state of California mandated a new program for chemically dependent and mentally ill physicians. The law established a diversion program under the direct control of the California State Board of Medical Quality Assurance, now the Medical Board of California (MBC), in recognition of the need for an alternate pathway to the usual disciplinary action taken against impaired physicians.[1] This alternative, including strict controls ensuring patient protection, allowed a physician to practice medicine, when possible, while receiving treatment and rehabilitation.

California and one other state, Oregon, allow their enforcement and disciplinary boards to administer such a program. In four other states, these are administered by an independent organization, with some form of representation and financial support from the medical board, medical society, or both. Three state programs are administered by medical societies through contractual arrangements with medical boards. All other state programs are administered by medical societies (Table 1).

The controversy over the appropriateness and effectiveness of a regulatory board administering a program for impaired physicians stems from the belief of some experts that physicians will not enter a program voluntarily because they will be frightened by the disciplinary aura of a state medical board. It is argued that physicians fear jeopardizing their license by being in any such program and, once in, may have difficulty with their rehabilitation because of this anxiety. Experience in California has proved otherwise.

## Organization of State Programs

In 1978 initial steps were taken in California to pass a new law for addicted or mentally ill physicians. The concept was new, and it became clear that for the public to feel secure about it, the MBC would have to play an active administrative role.

Despite the reservations of those who thought that any such program should be totally separate from the disciplinary and licensing board, legislation was passed in 1979 creating the diversion program under the MBC. When this legislation was passed, a sizable minority thought that the program should have been put under the auspices of the state medical association, while those in favor of diversion being under the MBC said that with the regulatory agency in charge, the public would not feel that "the foxes were again guarding the henhouse."[2]

Eight other states have created programs for impaired physicians through legislation. Most other state programs are administered through medical societies without specific legislation. Where laws have been mandated, the legislation has usually addressed such important issues as delineating areas of participant confidentiality and defining which cases are to be diverted from formal disciplinary action.

The nine legislatively mandated programs are administered by one of three organizations: state medical boards,[3] state medical societies,[4] or independent organizations.[5] No matter how it is administered, an impaired physician program has two major societal functions: to protect the public from impaired physicians and to rehabilitate chemically dependent or mentally ill physicians. At times these two functions may seem incompatible.

Programs administered by state disciplinary boards such as California's are argued to be less effective in reaching out to impaired physicians who do not have impending board actions against them. Physicians with chemical dependency or mental illness may not voluntarily join the impaired physicians program because of fear of becoming known to the medical disciplinary board. The advantage of this type of program should be that there is closer coordination with the licensing and disciplinary board, thus assuring public protection.

The programs administered by medical societies are argued to be more effective because impaired physicians will voluntarily join programs at an earlier stage of their disease. Physicians will purportedly do this because they will not feel threatened with potential discovery by the medical board. The drawback is that the disciplinary agency and the public

From the Diversion Program, Medical Board of California, Sacramento, California.
Reprint requests to Chet Pelton, Program Manager, Diversion Program, Medical Board of California, 1430 Howe Ave, Suite 84, Sacramento, CA 95825.

TABLE 1.—*Organizational Structure of State Impaired Physicians Programs*

| |
|---|
| Legislated programs administered by state medical boards |
| California |
| Oregon |
| Legislated programs administered by independent agencies |
| Colorado |
| Montana |
| New Mexico |
| Washington |
| Legislated programs administered by medical societies through contracts with medical boards |
| Alabama |
| Arizona |
| Florida |
| State programs administered by the medical societies |
| All other states |

may not feel they have enough information about physicians in the program to assure safety. State medical societies and state medical boards often become distrusting of each other.

In three states the medical societies administer the program through contractual agreements with medical boards. This seems to be some attempt at compromise.

In states where the program is administered by an independent organization, there is a further attempt at eliminating potential conflict in the first two models. Here the medical board and medical society are often represented on the governing board and provide some of the funding. Four state programs are currently administered in this manner (see Table 1).

In discussions at a 1989 conference of program directors from across the country, it was apparent that all states struggle with developing trust and coordination among the state medical societies, disciplinary boards, licensing boards, and the programs to rehabilitate physicians. This was even true of those programs administered by medical boards themselves.[6] Thus, the different models of organization did not appear to be the overriding factor in making a program effective. The question of organizational positioning seemed to create more grist for debate than to have any real importance in program outcome. The major factor was how organizational agencies representing the different entities worked together. In states where these agencies have developed trust and mutual respect, the programs work well indeed.[7]

## The California Program

Several elements make up California's diversion program. Each plays an important role in a physician's recovery. The administration of the diversion program coordinates all these elements.[8]

### *Diversion Evaluation Committee*

Each candidate to the diversion program is evaluated by a Diversion Evaluation Committee. This committee consists of four physicians and one public member, each an expert in the area of drug and alcohol addiction or mental illness. They volunteer an entire day every two months in the spirit of helping their colleagues find recovery. There are five such committees in California. For every addicted physician taken into the program, one of the members of the committee becomes the case consultant. The committee proposes a treatment plan for each physician in the form of an agreement. It must also determine whether these physicians are a danger to themselves or to the public. If, in the opinion of the Diversion Evaluation Committee there is no possibility of rehabilitation, the candidate will be rejected. This happens rarely, but it does happen.

### *Diversion Contract*

One of the standard features of the contract that is signed by the incoming candidate is that there will be no use of drugs or alcohol. This includes mind-altering prescription drugs if the participant is chemically dependent. Depending on the addiction involved, the taking of naltrexone hydrochloride or disulfiram may be required. In many instances, an inpatient treatment program of 28 to 30 days may be required. After that, two diversion group meetings each week are usually required, as well as two to four Alcoholics Anonymous meetings a week. Most contracts are for five years, but most candidates successfully complete the program in three years.

### *Diversion Group*

Groups comprise anywhere from 6 to 15 physicians. These groups are under the responsibility of skilled and experienced facilitators who are independent contractors in their relationship to the program and to the MBC. In the diversion group meetings, the emphasis is on the recovery process, the monitoring of behavior, and monitoring for the use of drugs and alcohol.

### *Case Manager*

The program relies on a case manager who is a full-time employee of the diversion program to monitor the progress of physicians' recovery. Each case manager is responsible for 50 to 60 physicians and their compliance with their agreements and progress toward developing a strong recovery program. The case manager is also responsible for taking necessary steps when a relapse occurs or other problems arise.

### *Hospital Well-being Committee or Condition Monitor*

Each physician who has hospital privileges must inform the hospital's Well-being Committee that he or she is in the program. The hospital committee, which has been mandated by law in California,[9] assists in the monitoring of a physician's recovery. The case manager works closely with each physician's well-being committee in monitoring recovery. When a physician does not have hospital privileges, a similar monitor is recruited at the physician's work site. This can be a colleague or trained person acceptable to the case manager.

Hospital well-being committees have been in existence for many years in a few hospitals in California. They have frequently intervened or otherwise motivated impaired physicians to enter the diversion program. After the new law mandated well-being committees at every California hospital, it was found that approximately 70% of hospitals had not previously had such committees. The new regulation is thus a major step in sensitizing hospitals and physicians about impairments and methods for intervention and treatment.

### *Board Enforcement Staff*

The investigative staff of the MBC is the intervening cause for 50% of physicians who enter the program. When an investigator becomes aware of an addiction problem, the physician in question may be given a choice of entering diversion or continuing with formal investigation and disciplinary

action. Most physicians choose to enter the diversion program rather than risk prosecution under the law.

Each element of the program plays a vital role in the successful rehabilitation of an addicted physician. The orchestration of these elements for physicians in need of help remains the administration's chief responsibility. Using the skills and collective experience of the administrative staff and the Diversion Evaluation Committee, programs are successfully tailored to the needs of each impaired physician entering diversion.

## Public Protection

A physician undergoing treatment will continue to work when it is safe and possible. This determination is a major responsibility of the Diversion Evaluation Committee when the physician is first evaluated. If the public would be at risk, the candidate is required to give up practice until the committee thinks that the physician in question can again work productively and safely. When a physician continues to practice, there are various levels of monitoring.

Once impaired physicians enter the program, they are assigned a case manager who will follow their progress. The case manager often consults with the case consultant, who is a member of the Diversion Evaluation Committee. The case manager will not only visit the impaired physician on occasion but will also take random urine or blood specimens, or both. As part of the contract, a physician initially attends a diversion group meeting twice a week. At these meetings the diversion group facilitator also monitors the physician's progress and will take random specimens of body fluids. As part of the total program, an impaired physician will attend two to four Alcoholics Anonymous meetings each week. At these meetings the candidate usually will obtain confirmation of attendance. A most critical but usually unmentioned monitoring tool is the diversion group itself. In addition to the facilitator, the group is composed of motivated, supportive, and caring colleagues who are often the first to know when things begin to go wrong again. At these times all the reserves of human resources around an impaired physician begin to work. This network of human contacts ensures patient protection and, where possible, continues the rehabilitation of the addicted physician in a conscientious and supportive fashion.

The Diversion Evaluation Committee may terminate a physician from diversion if he or she is not complying with the agreement or not developing a strong recovery program. If, at the time of termination, the committee determines the physician to be unsafe to practice medicine, the MBC is notified. The Enforcement Division of the MBC then takes appropriate investigatory and disciplinary action.[10]

## Rehabilitation

Two major rehabilitative features of the program are the incorporation of Alcoholics Anonymous, with its 12-step program, and the diversion groups with the facilitator. The practical side of diversion is that because a physician can work in most instances, there is a large economic saving to society. Physicians can remain productive and pay for their own treatment. Later, when they successfully complete the program, they become an important resource in dealing with society's major problem of addiction.

An unexpected finding from a recent unpublished survey of program participants is that most think that the strict structure and monitoring represent a positive feature of diversion. Many of these physicians commented that to be monitored with spot urine and other body fluid testing also gives them official, documented proof of their recovery.

Successful graduates from diversion on the whole become quite open about the fact of their disease. It has become a part of their conscious lives. It is considered part of their overall human experience and an important element in their own uniqueness.

## Ten-Year Results

In the past ten years, 618 doctors have entered California's diversion program; 244 have been successfully graduated, and 247 are currently enrolled (Table 2). Of these, 28 have withdrawn from the program and 57 were terminated for noncompliance. In addition, there has been the attrition of physicians leaving the state and those few who have died. The reasons for not completing the program are given in Table 3.

Approximately 50% of physicians in the program have

TABLE 2.—*Physicians in the California Diversion Program, January 1, 1990*

| | | Physicians, No. |
|---|---|---|
| Sex of participant | | |
| Male | | 225 |
| Female | | 22 |
| Current active participants | | 247 |
| Alcohol abuse | | 44 |
| Other drug abuse | | 120 |
| Alcohol and other drug abuse | | 63 |
| Mental illness | | 13 |
| Mental illness and substance abuse | | 6 |
| Physical illness | | 1 |
| Referral source | | |
| Board-referred participants (includes 19 physicians on probation) | | 124 |
| Non-board-referred participants | | 123 |
| Self | 57 | |
| Hospital | 27 | |
| Treatment facility | 15 | |
| Physician training programs | 9 | |
| Colleague | 5 | |
| Medical society | 2 | |
| Program participant | 1 | |
| Other | 7 | |
| | 123 | |

TABLE 3.—*Completion Versus Noncompletion, 1980 Through 1990 (n=371)*

| Outcome | Physicians, No. |
|---|---|
| Successful completion | 244 |
| Noncompletion | |
| Did not comply with program | 57 |
| Requested termination | 28 |
| Left state | 23 |
| Died | 13 |
| Put on probation | 2 |
| License revoked | 2 |
| Surrendered license | 2 |
| | 127 |

entered because an investigation was started or formal action was taken against them. The other half are considered self-referred, although someone—a colleague or hospital—may have strongly urged or even threatened them to enter the program. In the years before 1989, only 40% were self-referred. Thus, self-referrals now seem to be a growing trend, and we hope this is a reflection of a growing physician awarencss and acceptance of diversion.

## Recovery Effectiveness

Of physicians who started diversion, 72% completed it successfully. To successfully complete the program, a chemically dependent physician must be in diversion and free of alcohol and drugs for more than two years. Physicians must demonstrate a life-style that will support sobriety for the rest of their lives. This assessment is made by the five-member Diversion Evaluation Committee.

The effectiveness of the program is strongly influenced by the fact that there is strict monitoring of abstinence and meetings to deal with sobriety issues. The perceived threat of the loss of a physician's license remains a strong motivator to continue in a recovery program. If a person faithfully attends group meetings and Alcoholics Anonymous meetings and maintains sobriety, the recovery process has a good chance of working.

## Reaching Physicians With Problems

The California Diversion Program is not intended to be the sole resource for helping physicians who are chemically dependent or mentally ill. California physicians are encouraged to seek help from local chemical dependency treatment programs and local mental health therapists for mental disorders. Those physicians, however, who come under the scrutiny of the enforcement part of the MBC are required to participate. Even though the diversion program has an excellent recovery rate and has a strong monitoring system, we at the MBC think physicians should have the option of other recovery programs, as long as the public is being protected.

In addition to those 618 physicians who have been involved with the program, it is estimated that more than 650 other physicians have sought recovery from other treatment resources in the state of California. These estimates are from informal surveys conducted through local experts and known recovering physicians in specific areas of the state. The survey numbers were then projected statewide.

TABLE 4.—*High-Risk Specialties of Impaired Physicians*

| *Specialty* | *Licensed California Physicians, 1989, %** | *Physicians in Diversion Program, 1989, %* |
|---|---|---|
| Anesthesiologists | 5.0 | 17.4 |
| Radiology | 4.9 | 2.8 |
| Thoracic surgery | 0.4 | 0.4 |
| Plastic surgery | 1.0 | 0.8 |
| Neurology | 2.7 | 1.6 |
| Emergency medicine | 2.8 | 6.5 |
| General practice or family practice | 13.6 | 25.1 |
| Urology | 1.6 | 0.8 |
| Psychiatry | 6.9 | 6.5 |
| Obstetrics and gynecology | 6.1 | 6.0 |
| Internal medicine | 16.2 | 11.3 |
| Dermatology | 1.7 | 1.2 |
| Pathology | 2.5 | 1.2 |
| Surgery | 6.1 | 4.9 |
| Ophthalmology | 3.1 | 1.6 |
| Pediatrics | 7.2 | 4.5 |
| Other | 18.2 | 7.4 |

*Data obtained from the California Medical Association, May 1989.

## Unexpected Benefits

The diversion program has provided additional benefits that are not normally considered its objectives. These benefits go far beyond the primary objectives of patient protection and physician rehabilitation.

- The recovery process has the effect of changing a physician's quality of life beyond the use of alcohol and drugs. Physicians who complete the diversion program successfully have improved relationships with their patients, colleagues, and families.
- Physicians in the program have a better understanding of the disease of addiction and thus can help their patients with chemical dependency problems. Many experts think that recovering physicians are able to diagnose two to three times the number of patients with chemical dependency problems as are physicians who have not experienced alcohol or drug addiction.
- Recovering physicians reach out to help other physicians with a chemical dependency problem and are more skilled at knowing how to confront other physicians.
- A physician's recovery frequently forces family members to deal with their own dysfunction and personal issues. As a result, family members frequently begin to develop strong recovery programs of their own.

TABLE 5.—*Primary Drug Used by Anesthesiologists in the California Diversion Program*

| | |
|---|---|
| Fentanyl citrate | 17 |
| Meperidine (Demerol) HCl | 8 |
| Alcohol | 7 |
| Cocaine | 4 |
| Codeine | 2 |
| Morphine sulfate | 2 |
| Sedative | 1 |
| Diazepam (Valium) | 1 |
| Mental illness | 1 |
| Total | 43 |

HCl=hydrochloride

TABLE 6.—*Primary Drug Used by Participants in the California Diversion Program*

| *Drug* | *Users, No. (%)* |
|---|---|
| Alcohol | 85 ( 36) |
| Meperidine (Demerol) HCl | 33 ( 14) |
| Cocaine | 30 ( 13) |
| Fentanyl citrate | 17 ( 7) |
| Codeine | 13 ( 6) |
| Marijuana | 6 ( 3) |
| Amphetamines | 3 ( 1) |
| Morphine sulfate | 3 ( 1) |
| Alprazolam (Xanax) | 3 ( 1) |
| Oxycodone HCl and aspirin (Percodan) | 3 ( 1) |
| Other | 37 ( 17) |
| Total | 233 (100) |

HCl=hydrochloride

• Because the program is administered by a state agency, the problem of chemical dependence among physicians has come "out of the closet" and into the open for public scrutiny. This has made all Californians more aware that physicians are human, too, and are just as vulnerable to the disease of chemical dependence and mental illness.[11] The high recovery rate of physicians gives concrete proof that there is good prognosis for dealing with the disease.

## Current Enrollees

Table 4 lists the specialties of those currently enrolled in the program. The largest groups comprise anesthesiologists and family practitioners.[12]

Anesthesiology is at highest risk of all specialties in the diversion program. In comparing the number of anesthesiologists in the program with the number of licensed physicians in California who are anesthesiologists, their risk is 3.5 times greater than for the average physician.

In Table 5 the 43 anesthesiologists currently in the program list their first drug of choice. Because the diversion program also includes physicians with psychiatric problems, the one anesthesiologist with a mental problem is included.

Since the start of the diversion program, 127 physicians have failed to complete the program for various reasons (Table 3). The unsuccessful terminations are of concern and need more research.

A variety of drugs are used by participants in the program (Table 6). More than 81% of physicians with a drug abuse problem have indicated two or more drugs in their addiction. Of physicians who are alcoholic, 52% indicated they also used other drugs.

There are currently 13 physicians in the program who have mental illness as their primary problem, 4 each with bipolar affective disorders, depression, or a sexual disorder, and 1 diagnosed as psychotic. Six other physicians have mental illness as well as a chemical addiction.

## Conclusion

Despite initial skepticism of a state regulatory and disciplinary board administering a recovery program for addicted physicians, the ten-year record of California's diversion program within the MBC has been a success. The problem has not been the organizational positioning of the program within a regulatory agency charged with public protection. Instead, the challenge has been how to deal with the problem of chemical dependency in a rehabilitative manner that protects the public with high certainty.[13] The California Medical Association, the MBC, hospitals, and other medical organizations have worked together to face this challenge.

The California diversion program shows the major advantage gained when the public through open discussion is informed about the problem of physician impairment. The debates and discussion on impaired physicians have also helped public awareness and understanding about alcohol and drug problems in general.[14]

Half the physicians in the California program are motivated toward recovery in no small part because of the reality of potential licensure loss. This factor for them seems to have a definite therapeutic influence. It is hoped, however, that the focus of comparing state programs will shift from old arguments about organizational positioning to areas of meaningful discussion such as treatment and different motivations for recovery. Some possible areas of comparison and inquiry that may lead to valuable insights are as follows:

• How many licensed physicians are in various types of recovery programs, including organized impaired physicians programs, private programs, and Alcoholics Anonymous alone, and what are the long-term outcomes?

• What are the differences in monitoring techniques and their success in protecting the public and rehabilitating physicians?

• What are the rates of success and failure in rehabilitating physicians over their entire professional career?

This information is not yet available, and the common definitions for collecting comparable data have not been agreed on. Some states do not have the means to formally collect data, and others have sophisticated methods of collecting data. Some think these data inappropriate for public knowledge; others are mandated to report to the state legislature. There is a wide range of experience and philosophy.

Diversion programs are beginning to develop more experience in dealing with physicians with other problems, such as depression, bipolar affective disorders, sexual misconduct, high-risk behavior, and other obsessive-compulsive dysfunctions. With the basic organizational structure that has been developed, the programs are well positioned to meet new challenges in public protection and physician rehabilitation. As new ground is broken, a documented record of success, mutual respect, and trust remains the fundamental basis for further gains. Only through the cooperative efforts of medical societies, regulatory agencies, and the public can problem physicians be safely rehabilitated for all of society's benefit.

### REFERENCES

1. §2340 et seq, Article 14, Diversion Evaluation Committee, of the Cal Bus Profess Code, Medical Practice Act—Laws Relating to the Practice of Medicine and Surgery. Sacramento, Calif, Board of Medical Quality Assurance, 1989

2. Gualtieri AC, Cosentino JP, Becker JS: The California experience with a diversion program for impaired physicians. JAMA 1983; 249:226-229

3. Diversion Program for the Impaired Physician—Guidebook to Laws Governing the Practice of Medicine by Physicians and Surgeons. Sacramento, Calif, Board of Medical Quality Assurance, 1987

4. Impaired Practitioner Program of Florida: The Physician's Recovery Network (brochure). Jacksonville, Fla, Florida Medical Foundation, 1989

5. Casper E, Dilts SL, Soter JJ, et al: Establishment of the Colorado physician health program with a legislative initiative. JAMA 1988; 260:671-673

6. Report by the Auditor General: The Board of Medical Quality Assurance Has Made Progress in Improving Its Diversion Program; Some Problems Remain. Sacramento, Calif, Office of the Auditor General, 1986

7. Talbott GD, Benson EB: Impaired physicians: The dilemma of identification. Postgrad Med 1980; 68:56-63

8. BMQA's diversion program helps impaired MDs. Cal Phys 1988; 5:25

9. Physician Well-Being Committees. 22 CCR §§70703(d) and 71503(e)

10. Ikeda R: How BMQA reviews physicians: Cops and docs—Docs as cops. Cal Phys 1988; 5:36-37

11. Siegel BJ, Fitzgerald FT: A survey on the prevalence of alcoholism among the faculty and house staff of an academic teaching hospital. West J Med 1988; 148:593-595

12. Hyde GL: Management of the impaired person in the OR. Am Coll Surg Bull 1989; 74:6-9

13. Irons RR: New strategies on identification of impairment: The DUI campaign. Am Coll Surg Bull 1989; 74:9

14. Pischel ET: Impaired physicians don't have to go it alone. Cal Phys 1988; 5:22-25

# INFORMATION FOR AUTHORS

## Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, PO Box 7602, San Francisco, California 94120-7602. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar, and spelling.

### *Clinical Investigation Section*

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

## Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables, and references) on one side of the paper, with 1½-inch margins. Articles should not exceed 3,000 words (less than 15 text pages typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

### *Style*

*Abbreviations.* Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

*Weights and measures.* Use Système International (SI) units throughout the manuscript. Provide metric equivalents for all SI units; they will be noted parenthetically in the published text.

*Temperatures.* Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

*Drug names.* If the trade name of a drug is used, the generic name, including salt or ester, should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

### *Title Page*

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses, and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

### *Abstract*

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented," or "was investigated."

## Tables and Figures

### *Tables*

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title, and have its position indicated in the text.

### *Illustrations (Figures)*

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and the position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

### *Legends*

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

### *Permission for Reproduction*

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

## References

References should be limited to those cited in the text and should be to medical, scientific, or scholarly publications. (Mass circulation periodicals are referenced in parentheses in the text.) They must be typed double-spaced and numbered consecutively as they appear in the manuscript.* (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

### *Journal Articles*

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, use of inclusive page numbers, and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

### *Books*

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

### *Pamphlets, Monographs, or Books With No Given Author*

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

### *Articles in Press or Accepted for Publication*

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear and the phrase "in press" or "accepted for publication" in place of the date of publication.

### *Personal Communications and Unpublished Data*

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was oral or written, and the person's name, highest academic degree, and professional affiliation should be provided.

---

**Exception:* Articles for Topics in Primary Care and Epitomes use a limited number of authoritative references, both to the specific topic and the subject as a whole, that are *not* cited in the text and are listed in alphabetic order.

## Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

## Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians, or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects, and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

## Author Responsibility

Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously, and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

## Reprints

If reprints are desired, they must be paid for by the author. A reprint order form with schedule of prices is sent to the author when the article is published. Authors are responsible for handling requests for reprints of their articles.

Revised 10/1/87

# Our commitment to America's physicians: WE'RE IN IT TOGETHER.

Protect your practice with the financial strength only a national leader can provide. The Doctors' Company is the largest independent physician-owned and physician-governed professional liability insurer in America. We understand the issues you face and the concerns of practice management.

- Competitive premiums
- Risk management programs
- Tailored Group Practice programs with savings of 20% or more

An A+ (Q) (Superior) rating has been awarded The Doctors' Company by A.M. Best Company, independent analysts for the insurance industry. No higher rating is possible. We are endorsed by medical societies and associations throughout the nation.

Our primary reason for being is to meet your needs in these challenging times. As physicians ourselves, we would not envision doing anything less.

THE DOCTORS' COMPANY

More than 14,000 physicians call The Doctors' Company *their* company.

For referral to your local representative call:
(California) 800-352-7271 (Other States) 800-421-2368

Note: Not all specialties are insured in every state

CONTINUING MEDICAL EDUCATION

(Continued from Page 496)

June 10-16—**35th Annual Family Practice Review.** U of Colo at YMCA of the Rockies, Estes Park. One week. Contact: U of Colo.

June 30-July 3—**Renal Disease for the Internist and Nephrologist.** U of Colo at the Given Institute, Aspen. Sat-Tues. Contact: U of Colo.

July 8-13—**25th Annual Internal Medicine Program.** U of Colo at YMCA of the Rockies, Estes Park. Mon-Fri. Contact: U of Colo.

July 18-21—**Insulin Dependent Diabetes.** Barbara Davis Center for Childhood Diabetes, the Children's Diabetes Foundation, and CU School of Medicine at Keystone Inn, Keystone. Wed-Sat. Contact: U of Colo.

July 23-27—**3rd Annual Colorado Geriatric Symposium.** U of Colo at the Given Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 30-August 3—**Dynamic Psychotherapy.** U of Colo at the Given Institute, Aspen. Mon-Fri. Contact: U of Colo.

August 5-9—**Annual Pediatric Program.** U of Colo at the Given Institute, Aspen. Sun-Thurs. Contact: U of Colo.

August 12-18—**Annual Primary Care Orthopedics.** U of Colo at the Given Institute, Aspen. One week. Contact: U of Colo.

August 14-18—**Aspen Basic/Clinical Science: Neuroscience.** U of Colo at the Given Institute, Aspen. Tues-Sat. Contact: U of Colo.

August 20-24—**Annual Internal Medicine Board Review.** U of Colo, Denver. Mon-Fri. Contact: U of Colo.

September 10-14—**Family Practice Review.** U of Colo, Denver. Mon-Fri. Contact: U of Colo.

### CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

## IDAHO

May 17-19—**Idaho Academy of Family Physicians—Annual Meeting.** Red Lion Riverside, Boise. Thurs-Sat. Contact: Mrs Irma Sparks, Exec Dir, Idaho Academy of Family Physicians, PO Box 175, Boise 83701. (208) 362-4808.

July 26-28—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sun. Contact: Idaho Medical Association, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

## NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

May 4-5—**103rd Annual Meeting of the New Mexico Medical Society.** Albuquerque. Fri-Sat. Contact: Glenn Taylor, New Mexico Medical Society, 7770 Jefferson, NE, Albuquerque 87109. (505) 828-0237.

## UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

### MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

### SPONSORES OF COURSES—ABREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

(Continued on Page 626)

**ELECTRONIC CLAIMS SUBMISSION IS EASY, COST-EFFECTIVE AND MORE ACCURATE.**

# WHY AREN'T YOU USING IT?

With Blue Shield's ECS/EZ® system your claims submission is entirely automated. Standard Blue Shield and Medicare Part B (Blue Shield of California service areas) claims are transferred through the phone line (or tape) from your computer or your billing service to the information processing center.

Find out how ECS/EZ® can streamline your claims submissions at a lower cost by calling one of the many ECS/EZ® BLUE RIBBON billing services or office system vendors in your area TODAY!

ECS/EZ®
One Beach Street
San Francisco, CA 94133
℠ 415/445-5629

A Service of:

**Blue Shield**
of California

## OFFICE SYSTEMS

**Alcon Systems, Inc.**
800/289-1992

**Chen Information Systems, Inc.**
408/723-2343

**Computers For Medicine, Inc.**
714/687-6465

**DAL Associates, Inc.**
800/821-0890

**Electronic Medical Management, Inc.**
800/448-1333

**FastPay–SwiftWorks Corporation**
707/552-9110

**Medical Billing & Management Services**
800/448-1333

**Medical Dimensions**
415/283-5400

**PMW & Associates**
714/693-9504

**Professional Reimbursement**
415/222-0200

**Rx Computers, Inc.**
415/638-7475

**Spectral Data Systems**
415/751-6061

**Stratford Healthcare Systems Inc.**
415/692-7970

**VICOM, Inc.**
213/378-0898
800/999-8426

## BILLING SERVICES

**Doctors Billing Service**
805/324-4716

**Electronic Medical Management, Inc.**
800/448-1333

**Fran Allen's Physician's Billing Service**
619/342-4498

**M/D Systems, Inc.**
818/995-7111
800/272-3285

**Medical Billing & Management Services**
Stockton, CA
800/448-1333

**Medical Computer Billing**
916/966-9222

**Medical Data Services Inc.**
714/999-1397

**Medical Management Services**
916/332-7967

**Medical Systems, Inc.**
209/485-4800

**Our Billing Service**
707/823-4695

**Professional Billing & Management Services**
209/579-5628

**Professional Reimbursement**
415/222-0200

**Spectral Data Systems**
415/751-6061

**Versatile Management Services**
800/437-4242

**Wherrett & Associates, Inc.**
415/449-5400

**Woods Billing Service**
415/834-2622

## CLEARING HOUSES

**CIS Technologies, Inc.**
415/831-4857

**GTE Health Systems**
800/333-4362

**Physicians Practice Management**
800/428-3515

= offers standard Blue Shield in addition to Medicare

This advertisement is paid for in part by the organizations listed above and comprises a partial list of businesses approved to submit Standard Blue Shield and Medicare Part B claims to Blue Shield of California. ECS/EZ does not endorse any particular system, and encourages providers to research and select the system that is best for their particular business needs.

CONTINUING MEDICAL EDUCATION

*(Continued from Page 624)*

June 17-22—**School on Alcoholism and Other Drug Dependencies** (Sponsor: UUMC). Sun-Fri. University of Utah, Salt Lake City. Contact: (801) 538-3956.

July 8-14—**Update in Internal Medicine: Board Review Course** (Sponsor: UUMC). Sun-Sat. Cliff Lodge, Snowbird. Contact: (801) 581-8664.

July 25-27—**12th Annual Common Problems in Pediatrics** (Sponsor: UUMC). Wed-Fri. University Park Hotel, Salt Lake City. Contact: (801) 466-3500.

October 4-5—**Ethics and Health** (Sponsor: UUMC). Thurs-Sat. University of Utah Alumni House, Salt Lake City. Contact: (801) 581-8664.

## WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

May 18-19—**Applications of Doppler Ultrasound.** Seattle. Fri-Sat. Contact: VMMC.

June 8-9—**Common Anorectal Disorders: A Medical and Surgical Approach.** Seattle. Fri-Sat. Contact: VMMC.

June 14-15—**Orthopaedics.** Seattle. Thurs-Fri. Contact: Northwest Hospital, (206) 364-0500.

June 16—**AIDS Issues 1990.** Kirkland. Sat. Contact: Evergreen Hospital, (206) 823-7599.

June 25-26—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: CME Pierce County.

September 20—**Orthopedics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

October 11—**Diabetes.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

November 8—**Pediatrics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

### COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

## WYOMING

May 17-19—**Wyoming Academy of Family Physicians—Summer Meeting.** Auditorium, University of Wyoming Family Practice Residency Program, Casper. Thurs-Sat. Contact: Jay Swedberg, MD, 1522 East A St, Casper 82601. (307) 266-3076.

June 14-16—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

August 8-11—**American College of Surgeons, Montana—Wyoming Chapter.** Jackson Hole. Wed-Sat. Contact: Robert C. Ratcliff, MD, 940 E Third St, Casper 82601. (307) 577-4223. ◆


# This Publication is available in Microform.

**University Microfilms International**

Please send additional information

for _____
(name of publication)

Name_____

Institution_____

Street_____

City_____

State_____ Zip_____

300 North Zeeb Road
Dept. P.R.
Ann Arbor, Mi. 48106

*Because safety cannot be taken for granted in $H_2$-antagonist therapy*

# AXID®
## nizatidine

## *Minimal potential for drug interactions*

***Unlike cimetidine and ranitidine,[1] Axid does not inhibit the cytochrome P-450 metabolizing enzyme system.[2]***

## *Swift and effective $H_2$-antagonist therapy*

- *Most patients experience pain relief with the first dose[3]*
- *Heals duodenal ulcer rapidly and effectively[4,5]*
- *Dosage for adults with active duodenal ulcer is 300 mg once nightly (150 mg b.i.d. is also available)*


*References*
1. USP DI Update, September/October 1988, p 120.
2. Br J Clin Pharmacol 1985;20:710-713.
3. Data on file, Lilly Research Laboratories.
4. Scand J Gastroenterol 1987;22(suppl 136):61-70.
5. Am J Gastroenterol 1989;84:769-774.


**AXID®**
nizatidine capsules

**Brief Summary. Consult the package literature for complete information.**

**Indications and Usage:** 1. *Active duodenal ulcer*—for up to eight weeks of treatment. Most patients heal within four weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a reduced dosage of 150 mg h.s. The consequences of therapy with Axid for longer than one year are not known.

**Contraindication:** Known hypersensitivity to the drug. Use with caution in patients with hypersensitivity to other $H_2$-receptor antagonists.

**Precautions:** *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

*Laboratory Tests*—False-positive tests for urobilinogen with Multistix® may occur during therapy.

*Drug Interactions*—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

*Carcinogenesis, Mutagenesis, Impairment of Fertility*—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

*Pregnancy—Teratogenic Effects—Pregnancy Category C*—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Nursing Mothers*—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

*Pediatric Use*—Safety and effectiveness in children have not been established.

*Use in Elderly Patients*—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

**Adverse Reactions:** Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events was due to the drug.

*Hepatic*—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to three times the upper limit of normal, however, did not significantly differ from that in placebo patients. Hepatitis and jaundice have been reported. All abnormalities were reversible after discontinuation of Axid.

*Cardiovascular*—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

*CNS*—Rare cases of reversible mental confusion have been reported.

*Endocrine*—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

*Hematologic*—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another $H_2$-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

*Integumental*—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

*Hypersensitivity*—As with other $H_2$-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Because cross-sensitivity among this class has been observed, $H_2$-receptor antagonists should not be administered to those with a history of hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

*Other*—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

**Overdosage:** Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

PV 2098 AMP [091289]

*Additional information available to the profession on request.*

Lilly

**Eli Lilly and Company**
Indianapolis, Indiana
46285

NZ-2924-B-049310 ©1990, ELI LILLY AND COMPANY

# Classified Advertisements

The rate for each insertion is **$7 per line** (average six words per line) **with five lines ($35) minimum.** Confidential box number charge: $5 each month.

**Classified display rates $50 per inch. Maximum sizes: 1 column by 10 inches or 2 columns by 5 inches. Larger classified ad space by special arrangements.**

Copy for classified advertisements should be received not later than **25th of the second month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. Although The Western Journal of Medicine believes the classified advertisements in these columns to be from reputable sources, we do not investigate the offers made and assume no liability concerning them. The right is reserved to reject, withdraw, or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

**Please Type or Print Advertising Copy**

## Classified Advertisements Are Payable in Advance

CLASSIFIED ADVERTISEMENTS
THE WESTERN JOURNAL OF MEDICINE
P.O. BOX 7602, SAN FRANCISCO, CA 94120-7602
(415) 541-0900, ext. 376

### PHYSICIANS WANTED

**CALIFORNIA AND WESTERN STATES**
Opportunities for BE/BC physicians in metropolitan and rural areas in Cardiology, Critical Care, Emergency Medicine, Endocrinology, ENT, Family, General Surgery, Internal Medicine, Neurology, Neurosurgery, OB/GYN, Orthopedics, Pediatrics, Pulmonology, Rheumatology, and Urology. **Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.**

**NEAR STANFORD.** Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

**CALIFORNIA—NORTHERN.** Area's leading private practice group has immediate and future positions for BC/BE Family Practice and Primary Care Physicians in its Department of Ambulatory Care and General Medicine. Excellent compensation, incentive program, full benefits, early equity position, retirement plan. Experience life-style and professional fulfillment in beautiful northern California. Call Maureen Forrester: (408) 282-7833. Send CV to San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112.

**RADIOLOGIST.** Part-time position available immediately in small hospital with general radiography and fluoroscopy, mammography and ultrasound in Weaverville, California. Contact Drs Wheeler, Biggs, or Babbitt, West Coast Radiology, 3798 Janes Rd, Ste 12, Arcata, CA 95521; office number (707) 822-3621, ext 191.

**SAN FRANCISCO BAY AREA.** Full-time career Emergency Physician wanted for a high volume Emergency Department, 30 minutes south of San Francisco. Emergency Medicine BC/BE mandatory; prefer experienced. Congenial, democratic group of 20 full-time physicians doing some follow-up and minimal overnights. Competitive salary with excellent benefits including three to five weeks paid vacation; seven paid holidays; malpractice, medical, dental, and disability insurance; corporate shareholder in three years. Send CV or contact Drew Baker, MD, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545; (415) 784-4521.

### PHYSICIANS WANTED

**PHYSICIAN OPPORTUNITIES NATIONWIDE**
For all specialities for hospitals, clinics, multispecialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists. **Nugent & Grant, Inc, 1400 Coleman, Ste B-22, Santa Clara, CA 95090; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

**PHYSICIAN OPPORTUNITIES IN ARIZONA.** Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 90 plus physicians in Tucson, Green Valley, and Tempe, Arizona, has positions available in these cities in Internal Medicine, Pediatrics, OB/GYN, Orthopedics, Urgent Care, and Family Practice. Excellent fringe benefits and profit sharing program. Fee-for-service, as well as owned HMO. Must be BE/BC. Call or write James J. Vitali, CEO, Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732; (602) 322-8300.

**MD TO ASSIST** in busy Orthopedic clinic and Operating Room. Will also take call. Position has been used in the past as a bridge to Orthopedic residency. Attractive salary and excellent benefit package. Washington State licensure required. Available immediately. Send CV or contact Mary Anderson, Personnel Representative, Pacific Medical Center, 1200-12th Ave S., Seattle, WA 98144; (206) 326-4111.

**EUGENE CLINIC, EUGENE, OREGON**
Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Family Practice, Geriatrics, Occupational Medicine, Orthopedics, Psychiatry, Urgency Care, Urology. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

**Physician Recruiter**
**1162 Willamette St**
**Eugene, OR 97401**

### PHYSICIANS WANTED

**PHYSICIANS NEEDED**

The continuing growth of our service area population (now 90,000) has created an immediate need for additional BC/BE physicians in the following specialities:

- **ORTHOPEDIC SURGERY.** Establish your own private practice with no investment, guaranteed income. Exceptional income potential.
- **ONCOLOGY.** Establish private practice with no investment, guaranteed income. Some General Internal Medicine necessary initially.
- **RADIOLOGY.** Hospital group position. Excellent salary and benefit package. Competency in ultrasound, CAT, Nuclear Medicine, film screen mammography, and general diagnosis required. MRI experience desired. Inpatient and outpatient. (California license is required.)

Growing area with new businesses, stable economy. The California Department of Finance has predicted a 30 plus percent growth in population and jobs for our area during the decade of the 1990s.

112-bed full service hospital, very well equipped. Excellent ancillary services.

Located in central California near Sequoia National Park. Tulare offers a family oriented environment, abundant and varied recreation, good schools, restaurants, and shopping. Beautiful, affordable homes close to hospital and office. Strong economy. New businesses are contributing to the steady growth of our active community which combines the life-style advantages of a small city with easy access to all California attractions.

Contact:
**Tulare District Hospital**
**Physician Recruiting**
**Office, PO Box 90112**
**Los Angeles, CA 90009**
**(213) 216-2687**

**HAWAII.** Family Practitioner needed for rural underserved area. Full-time position in nonprofit community health clinic. No OB, hospitalizations optional. Desire dedicated person to work in multicultural setting. Contact Alan Chun, MD, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-7081.

**CALIFORNIA MULTISPECIALTY.** Cardiologist, Internal Medicine, Pediatrician, Endocrinologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist, Dermatologist, Ophthalmologist, General Surgeon, Podiatrist. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center—5, 17821 S. Pioneer Blvd, Artesia, CA 90701.

**INTERNAL MEDICINE.** Long established multispecialty group in central Washington needs Internist. Independent contract or join partnership later. University town with many cultural and recreational activities. Send CV to Medical Building Associates, 200 E. 6th, Ellensburg, WA 98926, or call (509) 925-9891.

**GYNECOLOGIST** needed for 78-bed JCAHO hospital. We are growing and we need to enlarge our specialty staff. Just opened new Cancer Treatment Center. 12,000 community, 90,000 immediate service area, 160,000 catchment area. Great outdoors area, cattle, oil, gas, hunting, fishing, good schools, low crime, ideal area for raising children. Reasonable malpractice rates. Send CV to Marilyn Bryan, Community Hospital, PO Box 2339, Elk City, OK 73648: (405) 225-2511.

*(Continued on Page 630)*

# PUT YOUR MEDICAL CAREER IN FLIGHT.

Discover the thrill of flying, the end of office overhead and the enjoyment of a general practice as an Air Force flight surgeon. Talk to an Air Force medical program manager about the tremendous benefits of being an Air Force medical officer:

- Quality lifestyle, quality practice
- 30 days vacation with pay per year
- Support of skilled professionals
- Non-contributing retirement plan if qualified

Discover how to take flight as an Air Force flight surgeon. Talk to the Air Force medical team today. Call

**USAF**
**HEALTH PROFESSIONS**
**TOLL FREE**
**1-800-423-USAF**

AIR FORCE

(Continued from Page 628)

PHYSICIANS WANTED

# PHYSICIANS
## REGISTERED PHYSICAL THERAPISTS PHYSICIAN ASSISTANT

Currently seeking California/Nevada state licensed BC/BE physicians and other medical professionals to perform Workers' Compensation and Personal Injury treatment and evaluation in our many California and Nevada locations. Spanish speaking a plus. Specialties include Neurology, Orthopedic, Internal Medicine, Psychiatry, Plastic Surgery, Occupational Medicine, Industrial Medicine.

We offer:

- Full-time or part-time
- Flexible hours
- Guaranteed income
- Possible expense for relocation
- Will provide training
- Excellent growth potential

Contact 1 (800) 347-2821

**FAMILY PRACTITIONER, NORTHERN CALIFORNIA.** Solo Family Practitioner (including OB) seeks BE/BC associate. English/Spanish preferred. Reasonable call. Beautiful "Redwood Empire" town, two hours from San Francisco. Guaranteed salary, benefits. Contact Andrew Coren, MD, 1165 S. Dora, E2, Ukiah, CA 95482; (707)463-3663.

**CENTRAL CALIFORNIA.** Join our team of Family Practice Physicians in a progressive community health center near Fresno, California. Competitive salary with extra on-call and overtime. Malpractice paid. Generous vacations and time-off policy. Affiliated with UCSF with on-site Family Practice residents and medical students. Varied practice, including Obstetrics, Pediatrics, and in-patient care with an emphasis on health maintenance, patient education, and primary care research. Position is 60 percent clinical, 40 percent teaching. Bilingual English-Spanish helpful. Contact Ardeth Bier, Fresno County Dept of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3353.

## GROWING, ESTABLISHED (1923)

35 physician multispecialty medical group with four locations in northeast central San Fernando Valley (north section of the Los Angeles City and County) seeks 1990/1991 BC/BE California licensed physicians in the following specialties:

INTERNAL MEDICINE
FAMILY PRACTICE
PEDIATRICS
OB/GYN
GENERAL SURGERY

Qualified candidates please send CV and references to:

**Mr Donald Abramsky, MBA**
**Administrator**
**Facey Medical Group, Inc.**
**11211 Sepulveda Blvd**
**Mission Hills, CA 91345-1196**
**(818) 365-9531**

PHYSICIANS WANTED

# WASHINGTON STATE
## ROCKWOOD CLINIC, PS

An expanding 70 physician multispecialty fee-for-service group seeks BC/BE physicians in the following specialties:

| | |
|---|---|
| ALLERGY | GASTROENTEROLOGY |
| CARDIOLOGY | HEMATOLOGY/ONCOLOGY |
| DERMATOLOGY | OB/GYN |
| INTERNAL MEDICINE | RHEUMATOLOGY |
| PEDIATRICS | GENERAL SURGERY |
| FAMILY PRACTICE | ORTHOPEDICS |

Attractive benefit package includes competitive salary leading to early shareholder status.

CONTACT: **Colleen Mooney, Recruitment Coordinator**
**Rockwood Clinic, PS**
**E. 400 Fifth Ave**
**Spokane, WA 99202**
**(509) 838-2531**

**COME ENJOY SPOKANE'S QUALITY LIFE-STYLE!**

**SAN FRANCISCO BAY AREA.** BE/BC Internist. We currently are seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 prepaid Health Plan members. Recently renovated and expanded medical center facilities are within convenient communting distance to virtually any bay area city and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to Winslow Wong, MD, Attn: Administration, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545. EOE.

**NORTHERN CALIFORNIA—SAN FRANCISCO BAY AREA.** Leading HMO is seeking BC/BE physician to staff a busy urban, full-service Emergency Department with the possibility of administrative advancement. Kaiser Permanente is a large prepaid HMO offering competitive salary, job security, shareholder status, and generous benefits including health care, life insurance, disability insurance, sick leave, mortgage assistance, and educational leave. Please address all inquiries to David Witt, MD, Emergency Dept, Kaiser Permanente Medical Center, 1200 El Camino Real, South San Francisco, CA 94080-3299; or call (415) 742-2516. EOE.

**FAMILY PRACTICE PHYSICIAN.** Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

**ARIZONA.** Established Emergency Medicine group has immediate openings for full- or part-time BC/BE physicians seeking career opportunity in busy Emergency Department with excellent location and case mix. Flexible schedules, excellent living and working conditions. Compensation range $150K to $200K for full-time. Send CV in confidence to General Manager, PO Box 80412, Phoenix, AZ 85060-0412.

**URGENT CARE PHYSICIAN.** Full- or part-time position available for northern California urgent care clinic. Contact David Lyons, MD, 900 Oro Dam Blvd, Oroville, CA 95991; (916) 534-9183.

KAISER PERMANENTE
*Good People. Good Medicine.*

## NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

**MULTIPLE FAMILY PRACTICE** (BC/BE) positions available in several suburban satellite clinics of a large Seattle area multispecialty group practice. Diverse patient population includes managed care, fee-for-service, and retired military (at some satellite clinics). Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

**SACRAMENTO KAISER PERMANENTE.** BC/BE Family Practitioners needed to join large group of Family Practitioners providing ambulatory and in-patient care in a large prepaid health plan. Excellent working environment with strong specialty support. Outstanding financial package. Sacramento is a growing metropolitan area with good schools and recreational activities. Close to San Francisco and Lake Tahoe. If interested, please contact Stuart Hahn, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825; or call (916) 973-5546. EOE.

(Continued on Page 632)

# The Permanente Medical Group
## Northern California

**Quality**

**Stability**

**Leadership**

**Growth**

**Support**

**Rewards**

The Permanente Medical Group, the largest multispecialty group practice in the U.S., is undergoing explosive growth in its Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley. Our rapid increase in membership has created practice opportunities throughout the region.

Our physician-managed group is part of the comprehensive Kaiser Permanente Medical Care Program. As a TPMG physician, you have access to the latest medical technology and resources, the support of colleagues in all subspecialties — and the opportunity to provide excellent health care without the burdens of managing a practice.

Join us in one of these facilities:

- Walnut Creek/Pleasanton
- Martinez/Antioch
- Oakland
- South Sacramento/Stockton
- Santa Rosa
- San Jose/Gilroy
- San Francisco
- South San Francisco
- Sacramento/Roseville
- Richmond
- Redwood City
- Fresno
- Hayward/Fremont
- Santa Clara/Milpitas/Sunnyvale
- Vallejo/Fairfield/Napa
- San Rafael/Petaluma

TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, continuing education, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. For complete information, call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-7155, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800) 777-4912. EOE

KAISER PERMANENTE
*Good People. Good Medicine.*

(Continued from Page 630)

PHYSICIANS WANTED

# PHYSICIANS

## PRIMARY CARE

### CALIFORNIA

JSA, Inc. is currently offering physicians full, part-time, and PRN positions in Primary Care Clinics located in San Diego and Sacramento.

**BENEFITS PACKAGE**

- **Flexible day-time hours**
- **No "on-call" requirement**
- **Malpractice insurance reimbursement**
- **Professional development funding**
- **Incentive programs**
- **Exceptional salary level**

**QUALIFICATIONS**

- **BC or graduate of an approved residency program in a Primary Care Specialty**
- **MD or DO**
- **Current state licensure**
- **ACLS/BCLS**

A proposed project in Oceanside includes positions in Emergency Medicine and Primary Care Specialties.

For further information, please contact Susan Bray, Recruiting Director at (301) 964-2811. JSA, Inc., PO Box 1305, Columbia, MD 21044.

JSA

HEALTHCARE

Consulting - Management - Services

An Equal Opportunity Employer

**CALIFORNIA NORTHERN.** A stable group of four ABEM certified/eligible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klammath, Rogue, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1000, San Francisco, CA 94104.

**URGENT CARE/PRIMARY CARE PHYSICIANS** for over 90 positions available with various physician groups in Phoenix metropolitan/Tucson, Arizona. Excellent compensation and partnership opportunities. Contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

**IMMEDIATE OPENING.** University affiliated ambulatory center. Full-time position available immediately in San Bernardino/Riverside, California. Competitive basic salary guarantee plus attractive fringe benefits. Contact Daniel Injo, MD, 22182 Barton Rd, Grand Terrace, CA 92324; (714) 370-1300.

**NORTHERN CALIFORNIA—SACRAMENTO.** Leading HMO is seeking a BC/BE inpatient and outpatient Family Practitioner. Inpatient responsibility extends to physicians' individual practice only. Emphasis on Internal Medicine, Gynecology, and Orthopedics. No OB, limited Pediatrics. Must work outpatient clinic one night per week and one weekend day per month. We offer many benefits including malpractice insurance, medical, dental, and group life insurance, vacation, sick, and educational leave, excellent retirement benefits, and special arrangements for physicians transferring from established practice. For more information, please send CV to Dr J. Berger, Kaiser Permanente Medical Center, 6600 Bruceville Rd, Sacramento, CA 95823. EOE.

**WASHINGTON.** BC/BE General Internists to join expanding 32 physician multispecialty group located in the foothills of the Blue Mountains. Excellent schools, cultural, and recreational opportunities. One junior college and two four-year colleges are located in the community. Guaranteed income with excellent benefit program. Send CV to Connie Goude, 55 W. Tietan, Walla Walla, WA 99362.

**AMBULATORY CARE.** Full-time/part-time openings, northern, southern, and central locations. Competitive salary, strong incentive package, and growth potential. Malpractice paid. Join our partnership of established Emergency Medicine and Ambulatory Care Physicians. Contact Jane Dressler, California Emergency Physicians, 2101 Webster St, Ste 1050, Oakland, CA 94612-3027; (415) 835-7431 or (800) 842-2619.

**EXCEPTIONAL SOLO PRACTICE OPPORTUNITY** for a Psychiatrist. Located in southeastern Utah in the city of Price, near scenic national parks, great skiing, and other outdoor recreation. Excellent educational facilities including a junior college. Primary service area is approximately 30,000 people. Contact Tad Morley, Castleview Hospital, 300 N. Hospital Dr, Price, UT 84501; (801) 637-4800.

**CALIFORNIA LICENSED BC RADIOLOGIST** for back-up locum tenens, plus potential full-time. Contact I.V. Radiology Medical Group, 1266 Pepper Dr, El Centro, CA 92243; (619) 352-5666 after 6 pm.

**GENERAL INTERNIST.** Multispecialty group located in San Luis Obispo, California, seeks a BC/BE physician. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to Physician Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

## SOUTHERN CALIFORNIA

Specialists and Primary Care Physicians—CIGNA Healthplans invites you to join our innovative and dynamic managed health care team. Our multidisciplinary HMO practice provides a supportive and collegial work environment at 31 locations. You will enjoy a wealth of cultural and recreational activities, access to major academic centers, and an excellent compensation package. *Call collect* **(818) 500-6570 or send CV to Robert Harrington, MD, Professional Recruitment, CIGNA Healthplans of California, 505 N. Brand Blvd, Ste 400-49, Glendale, CA 91203.**

PHYSICIANS WANTED

# Physician Administrator

## Southern California

CIGNA Healthplans of California - a staff model HMO committed to providing innovative, quality health care to 400,000 members in Southern California - is seeking a physician to assume the challenging responsibilities of Physician Administrator at one of our 30 health care centers.

You will maintain an active clinical practice with a proportion of time dedicated to leadership and management of physician and support staff. Qualifications include Board Certification in a clinical specialty and management experience. Excellent compensation and benefit package, including bonus plan. Call collect **(818) 500-6570** or send CV in confidence to: **Robert Harrington, MD, Professional Recruitment Department, CIGNA Healthplans of California, 505 N. Brand Boulevard, Suite 400-49, Glendale, CA 91203.** Equal Opportunity Employer.

CIGNA Healthplan Team with results™

CIGNA

**SAN JOSE, CALIFORNIA.** Urgent Care. Positions currently available for experienced physicians to provide primary care services at hospital based Urgent Care Center in San Jose. Minimum guarantee of $100,00 plus annual for 42 hour work week and paid malpractice. No night call. Please contact Nanette Peter at AEP, (408) 293-8881.

**NORTHERN CALIFORNIA.** The Permanente Medical Group, Inc, has immediate openings for BC/BE General Internists at the Roseville facility. Kaiser Permanente is a leader in health care, providing quality medical care to a rapidly growing population. We offer a tremendous benefit package and starting salary for career oriented physicians. Roseville is a foothill community located 90 miles from San Francisco and 100 miles from Lake Tahoe and Sierra skiing. University affiliation and teaching appointments are available. Send CV to Tony Cantelmi, MD, The Permanente Medical Group, Inc, 1001 Riverside Blvd, Roseville, CA 95678. EOE.

**BC/BE INTERNIST** needed to practice Intensive Care Medicine for a busy, moderate-sized, multispecialty group practice, 25 miles south of San Francisco. Majority of practice based at a 400-bed state-of-the-art hospital, adjacent to the clinic. Excellent salary, vacation, and benefits. Ideal for recently BC/BE Internists awaiting fellowships in July 1991 for Pulmonary, Cardiology, or Critical Care Medicine. Send CV to Number 198, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**PEDIATRICIAN BC/BE** needed to join four physician department in busy, moderate sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 198, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

(Continued on Page 633)

(Continued from Page 632)

PHYSICIANS WANTED

# Join us.

**PACIFIC NORTHWEST**
**Group Health Cooperative of Puget Sound**

One of the nation's largest and oldest HMOs currently has permanent and locum tenens positions available for:

- Family Practitioners
- Pediatricians
- Physician Assistants
- Psychiatrist–General
- Psychiatrist–Child
- Psychologist

To inquire, write:
Manager, Medical Staff Personnel
Group Health Cooperative of Puget Sound
521 Wall Street
Seattle, WA 98121

or call (206) 448-6546

PHYSICIANS WANTED

## MEMORIAL GENERAL HOSPITAL
## LAS CRUCES, NEW MEXICO

# MODEL OB PRACTICE

Needs OB/GYN to join 2 obstetricians and 3 certified nurse midwives to provide OB/GYN services to the underprivileged women of the area.

286 beds • Acute care facility with level II nursery • Excellent pediatric support • Nestled between the beautiful Rio Grande Valley and the majestic Organ Mountains • World class skiing • Water sports • Beautiful weather • Located in a university town • Named one of the top ten fastest growing cities in the country

Prefer BE/BC practitioner with ultrasound, colposcopy, high risk obstetrical experience. Salary, malpractice, benefits.

Please call: (505) 521-2258

(Continued on Page 634)

# YOUR SPECIALTY IS WORTH AN EXTRA $8,000 A YEAR.

If you're a resident in any of the following specialties:

- anesthesiology
- orthopedic surgery
- general surgery
- neurosurgery
- colon/rectal surgery
- cardiac/thoracic surgery
- pediatric surgery
- peripheral/vascular surgery
- plastic surgery

you could be eligible for an $8,000 annual stipend in the Army Reserve's Specialized Training Assistance Program.

You'll also be using your skills in a variety of challenging settings, from major medical centers to field hospitals, and there are opportunities for conferences and continuing education.

We know your time is valuable, so we'll be flexible about the time you serve. Your immediate commitment could be as little as two weeks a year, with a small added obligation later on. If you'd like to talk to an Army Reserve physician, or if you'd like more information about the stipend program or other medical opportunities, call our experienced Army Reserve Medical Counselor:

MAJOR MARISSA PARKER, (415) 883-8852/8985
MAJOR JANE MEYER, (415) 922-8985/8986

**BE ALL YOU CAN BE.®**
**ARMY RESERVE**

(Continued from Page 633)

PHYSICIANS WANTED

*Join the leader and enjoy your practice!*

## Family Practice

Pacific Physician Services
A dynamic and growing 65-physician Southern California medical group network, has immediate career opportunities for primary care physicians. Examine our benefits:

- $8K monthly guarantee;
- Monthly FFS productivity incentives;
- Paid malpractice;
- Medical & dental plans;
- Retirement, disability;
- Vacation, CME, sick time.

Discover an enjoyable practice, call

Ruthan Smith
(800) 338-4798
or (714) 825-4401 in CA

**INTERNIST BC/BE** needed to join thirteen physician department in busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Excellent salary, vacation, and benefits. Early partnership. Please send CV to Number 198, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**OB/GYN.** Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

**NATIONAL HAIR TRANSPLANT COMPANY** seeks physician with MD degree to perform hair restoration surgery in the west coast states. Excellent compensation and benefit package. Will train in new techniques. Good opportunity for a physician looking for a change in daily routine. Send CV to Richard P. Giannotti, MD, PC, Pembroke Four Building, Ste 210, Virginia Beach, VA 23462.

**CALIFORNIA, SANTA CLARA COUNTY.** Positions currently available for experienced physicians to provide primary care services at hospital based Urgent Care Center in San Jose. Minimum guarantee of $100,000 plus annual for 42-hour work week, 48 weeks per year with paid malpractice. No night call. Please contact Nanette Peter, Associated Emergency Physicians, Inc, Medical Group of Northern California, 1625 The Alameda, Ste 201, San Jose, CA 95126; (408) 293-8881.

**ALBUQUERQUE, NEW MEXICO.** BC/BE Family Practitioners sought to join established, private practice, single specialty group practice. Income guarantee, benefits. Please send CV to Kathryn Rhoades, Presbyterian Healthcare Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 6330.

PHYSICIANS WANTED

**LONGVIEW, WASHINGTON**

KAISER PERMANENTE
NORTHWEST PERMANENTE P.C. PHYSICIANS AND SURGEONS

**IMMEDIATE PHYSICIAN OPENINGS**

Rapidly growing all family practice clinic. Local community specialty support. No obstetrics.
CV to: Regional Medical Director
Northwest Permanente P.C.
3600 N. Interstate Ave. Portland, OR 97227

★LONGVIEW

Longview is a picturesque, stable community of 42,000 located near the Columbia Gorge and the coastal mountains and beaches of Washington and Oregon. Members of our 12 physician group enjoy individual subpractices, infrequent call, and excellent facilities in our new clinic. We invite you to contact us regarding practice opportunities.

SMA

Southwest Medical Associates
A Sierra Health Services Company

## ENDOCRINOLOGIST / NEUROLOGIST

An opportunity is waiting for you with Nevada's oldest and largest multi-specialty Group Practice. We have immediate openings for highly qualified physicians in the specializations of Endocrinology and Neurology.

Las Vegas has a rapidly growing (750,000 +) population, mild climate, affordable housing, no state income tax, plus abundant recreational and cultural activities.

Excellent compensation and benefits package including:
- **401K • Stock option plan • Paid malpractice • C.M.E.**
- **Relocation expenses**

*If you are interested in an exciting and financially rewarding opportunity in a progressive health care organization, please forward your C.V. to: Janet R. Bishop, Manager, Physician Recruitment, Southwest Medical Associates, P.O. Box 15645, Las Vegas, NV 89114-5645.*

**FAMILY PRACTITIONER.** Multispecialty group located in San Luis Obispo, California, seeks a BC/BE physician. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to Physician Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

**BC/BE INTERNAL MEDICINE** physician for Primary Care group practice in growing Fresno Community. Well orchestrated/staffed office with associated lab. Contact Michael W. Lynch, MD, 5151 N. Palm, Ste 200, Fresno, CA 93704; (209) 229-2786.

**OB/GYN, INTERNISTS,** Family Practitioners, Pediatricians for Arizona and western opportunities. Quality positions available other regions of country. Inquiries confidential. Mitchell & Associates, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

**FULL-TIME TRAVEL REQUIRED** (one year minimum). Health research organization needs physicians for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individuals will be part of a large medical team conducting health examinations in government examination centers traveling to 88 areas of the US through 1993. Physicians must be licensed in one state and specialized in Internal or Family Medicine. Competitive salaries, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline at (800) 937-8281, ext 8248. Westat, Inc, Rockville, MD. EOE/M/F/V/H.

**BC/BE ORTHOPEDIC SURGEON** needed to join two physician department in a busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to a 400-bed, state-of-the-art hospital. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 198, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**SAN FRANCISCO BAY AREA** multispecialty group seeks Pediatrician BC/BE, to join 26 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Daniel Rowe, MD, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

**OREGON.** Family Practice opportunity in sunny southern Oregon. Three physicians seeking two associates, so bring a colleague! No Obstetrics. Great quality of life. Contact Mark Wood, Klamath Family Practice, (503) 883-8134.

**SAN DIEGO, CALIFORNIA.** Immediate opportunities for Family Practitioners: Urgent Care, Ambulatory Care, or General/Family Medicine. Group or solo, potential partnership or purchase, income guarantees. Contact Paul Byerlein, Jackson and Coker, 115 Perimeter Center Pl, Ste 380 WJM0, Atlanta, GA 30346; 1 (800) 544-1987 or 1 (800) 888-5530.

(Continued on Page 635)

(Continued from Page 634)

PHYSICIANS WANTED

## EXCELLENT
# FAMILY PRACTICE
## OPPORTUNITY

ROCKWOOD CLINIC, P.S.—a network of Family Practice clinics (main building and six satellites) seeks BE/BC Family Practitioners to join these busy independent practices offering the full range of inpatient/outpatient services, including obstetrics. ADVANTAGES INCLUDE:

- Join the largest department within this multispecialty group (15 Family Practitioners)
- Immediate in-house specialty consultation
- Well trained administrative support to assist in business matters, while allowing autonomy regarding the decisions of your practice
- Attractive benefit package includes excellent salary leading to early shareholder status

SPOKANE, WASHINGTON (metropolitan population 350,000), offers very affordable housing, unlimited year-round recreation, excellent schools, and numerous cultural organizations.

CONTACT:
**Colleen Mooney**
**Recruitment Coordinator**
**Rockwood Clinic**
**E. 400 Fifth Ave**
**Spokane, WA 99202**
**(509) 838-2531**

**CALIFORNIA, MOTHER LODE COUNTRY.** Family Practice, General Practice, in rural community health center. Excellent recreation area. Send CV or contact Randy Windsor, Executive Director, PO Box 897, Pioneer, CA 95666; (209) 295-5544.

**PEDIATRICIAN BC/BE** needed in northern suburb of San Francisco. Opportunity to join part of a multispecialty group. Applicant should demonstrate strong academic skills committed to quality personalized care. Forward CV to Peter Earley, Physician Relations, Ross Valley Medical Group, 2200 Larkspur Landing Circle, Ste 103, Larkspur, CA 94939.

**FAMILY PRACTITIONER.** At last an opportunity to make a difference. Primary Care Physician needed in order to provide care for multiple challenging medical problems. Part-time or full-time positions available. Hours negotiable, Family Practice (FP) or Internist (IM) and Pediatricians preferred. Please contact Medical Director, Dr Williams at (415) 233-3994, ext 467.

**FAMILY PRACTITIONER, BC/BE** to join well established multispecialty group on northern California coast. Salaried position leading to partnership after one year. Opportunity to help build Family Practice department/Primary Care center. Prefer OB, as established Family Practitioner does OB. Spanish language helpful. CV to Connie Kellough, Administrator, Watsonville Medical Group, 850 Freedom Blvd, Watsonville, CA 95076.

PHYSICIANS WANTED

## CALIFORNIA

Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Carol Sweig or Jim Ellis, Directors, (415) 673-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (818) 999-1050 or (800) 635-3175.**

**SOUTHERN CALIFORNIA.** BC/BE Internists and Family Practitioners for oceanside, smog-free community. Well kept secret! Join established group or solo with coverage. Share call/coverage. 258-bed hospital with strong ancillary services and excellent location. Competitive financial package, partnership, interviewing and relocation expenses. Contact Paul Byerlein, Jackson and Coker, 115 Perimeter Center Pl, Ste 380 WJM0, Atlanta, GA 30346; 1 (800) 544-1987 or 1 (800) 888-5530.

**INTERNAL MEDICINE PARTNERSHIP OPPORTUNITY.** Join well established multispecialty group in beautiful Lincoln, Nebraska. Clinic boasts advanced Radiology department and progressive certified lab. Recognized resources for open heart surgery, transplants, and Neurosurgery. Be busy immediately. Enjoy time off with easy one in four call. University town offers culture, shopping, dining, and sporting events. Omaha less than one hour away offers big city amenities. Generous salary plus bonus and benefits for two years—then partnership; season tickets to highly coveted University of Nebraska "Big Red" games. Contact Bryan Bassett, Jackson and Coker, 115 Perimeter Center Pl, Ste 380 WJM0, Atlanta, GA 30346; 1 (800) 544-1987 or 1 (800) 288-7030.

**SAN FRANCISCO.** Free medical clinic serving the homeless and the underserved. Looking for a Family Physician or Primary Care Internist to work 24 to 32 hours per week. Send résumé to Robin Serrahn, MD, 105 Golden Gate Ave, San Francisco, CA 94102.

**INTERNIST, PORTLAND, OREGON.** Well established practice needs associate. Life-style, nutrition, fitness oriented. Interesting, varied, Internal Medicine plus health promotion for business and organizations. Letters of application to Number 204, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**RESEARCH ASSOCIATE.** Facilitate and coordinate Anesthesiology research projects to study action of drugs, serums, and hormones on lab animals, perform and assist laboratory and clinical experiments, record results. Research neuromuscular pharmacology and physiology. Requires PhD or MD in Clinical Medicine and three years experience in job offer or three years research work. Requires experience with anesthesia equipment, clinical anesthesia, and neuromuscular minitors. $646.73 per week. Job/interview: Torrance. Send ad and résumé to JOB#KV13919, PO Box 9560, Sacramento, CA 95823-9560 not later than June 30, 1990.

**FAMILY PRACTICE OPPORTUNITY.** Association available in rural town, one hour from Seattle and one-half hour from Tacoma, Obstetrics optional. Growing community close to mountains and Puget Sound. Owner to retire in four to five years. (206) 829-1444.

**PEDIATRICIAN, BC/BE** to join busy, well established Pediatric practice in San Francisco suburb. Two Pediatricians looking for two full-/part-time associates to replace two retiring partners. Guaranteed salary leading to early partnership. Flexible hours possible. Large patient base means you can be busy from first day. Excellent hospitals with neonatal and pediatric ICUs. University appointments possible. Beautiful San Francisco bay area convenient to ski areas, beaches, wine country. Gerald Harris, MD, Pediatric Medical Group, 1800 Sullivan Ave, Ste 507, Daly City, CA 94015; (415) 756-5150.

**VACAVILLE, CALIFORNIA.** Excellent Family Practice opportunity for BC/BE in three person group. Guaranteed salary with buy in after one year. Suburban community close to recreation. Contact R. B. Rushford, MD, 601 Buck Ave, Vacaville, CA 95688.

PHYSICIANS WANTED

## Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services
5414 E. Montecito, Fresno, CA 93727
Or call 1 (800) 873-0786

**INTERNIST, PEDIATRICIAN** to join multispecialty group. Salary with incentive, early partnership. Northern California. Reply to Number 197, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**WENATCHEE, WASHINGTON, PACIFIC NORTHWEST.** Wenatchee Valley Clinic, a 95-physician multispecialty clinic, is seeking a BC/BE General Internist. Guaranteed first year salary, incentive production bonus available. Attractive fringe benefit package. Located on the Columbia River in the sunny eastern foothills of the Cascades. Abundant recreational activities available. Send résumés to Wenatchee Valley Clinic, PO Box 489, Wenatchee, WA 98807, Attn: Julie Zimmerman.

**OB/GYN.** BC/BE to join 20 physician (OB, Pediatrics, Internal Medicine) practice in sunny central Washington. Reasonable call schedule with three OB/GYN department. Competitive salary, excellent benefit package including vacation at 30 days per year and professional liability. Contact Ann Garza, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

**PATHOLOGY DIRECTOR / SOUTHERN CALIFORNIA.** California-licensed, clinically/anatomically trained with three to five years community hospital director experience needed to run Pathology department in 230-bed community hospital. Beautiful beach location in moderate sized city with excellent outdoor activity opportunities. Send CV to Administration, Community Memorial Hospital, Loma Vista at Brent, Ventura, CA 93003; or call (805) 652-5005.

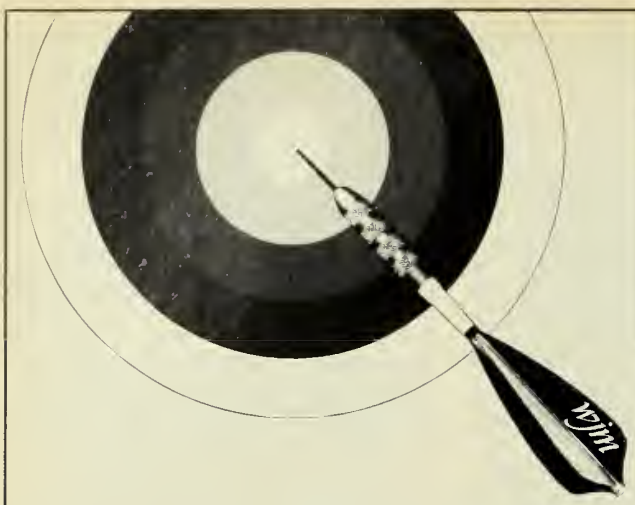
**PEDIATRICIAN, BC/BE, LOS ANGELES.** Full-time position at a private, nonprofit downtown university affiliated hospital with busy clinic. Compensation starts at $85,000 (BE) to $95,000 (BC) plus benefits and opportunities for advancement. On call every fourth night, every fourth weekend. Clinic serves children of normal intellectual range with challenging chronic diseases. Treatment team approach includes nurses, social workers, physical therapists. Many indigent patients subsidized by a private foundation. Send CV to Rosemary Hutton, 2400 S. Flower St, Los Angeles, CA 90007.

**FAMILY PRACTICE. BC/BE CALIFORNIA.** Position offers excellent salary and comprehensive benefit package in desirable central California location. Multispecialty group practice sponsored by County with all inpatient work done in private hospitals. Located near Sequoia National Park. Family oriented life-style; good schools, restaurants, shopping. Easy access to metropolitan areas and California attractions. California license required. Contact Tulare District Hospital Physician Recruiting Office, Box 90112, Los Angeles, CA 90009; (213) 216-2687.

**NORTHERN CALIFORNIA.** Multispecialty group in central valley community 60 miles east of San Francisco seeks well-trained OB/GYN, Cardiologist, ENT, Pediatrician, and Neurologist. Growing community 32,000 in rural-suburban setting offers reasonable housing costs, good schools, and nearby recreational areas. Ken Baker, PSG, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

**SOUTHERN CALIFORNIA.** Young Family Practitioner with dynamic practice seeking associate for future partnership. Generous salary/guarantee and incentives package. New medical office near outstanding 300-bed community hospital. Growing community within one hour of beaches and mountains. Ken Baker, PSG, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

(Continued on Page 637)




# right on TARGET

Consider a few features of **The Western Journal of Medicine:**

- **Epitomes of Progress**
  Each month this selection highlights the major advances in a different specialty with 15 or 20 brief epitomes by experts in the field.
- **Clinical Investigation**
  Five major clinical research societies coordinate important new research findings, emphasizing clinical value.
- **Socioeconomics**
  WJM is often the first to predict, examine, and evaluate socioeconomic changes and trends.
- **Yearly Special Issue**
  Each devoted to a topic vital to physicians: cross-cultural medicine (1983), personal health maintenance (1984), high-tech medicine (1985), medical informatics (1986), AIDS—a global perspective (1987), women and medicine (1988).

Enclosed is $_____ to cover _____ subscriptions.

Subscription renewal ☐ Regular subscription ☐

Foreign subscription ☐ Bill me ☐

Student ☐ Resident ☐

TO: _____

Street _____

City/State/Zip _____

Specialty (If applicable) _____

Student/Resident Completion Date (Year) _____

Please mail this coupon with enclosed payment to:

**Circulation Department**
P.O. Box 7602, San Francisco
California 94120-7602

Subscriptions, 12 issues per year
U.S. and Canada: $30 1 year, $50 2 years
All other countries: $50 1 year, $90 2 years
Student/Resident (USA and Canada): $15 per year

**The Western Journal of Medicine**

**P.O. Box 7602 • San Francisco, California 94120-7602**
**(415) 882-5179**



# USING IT WON'T KILL YOU. NOT USING IT MIGHT.

Maybe you don't like using condoms. But if you're going to have sex, a latex condom with a spermicide is your best protection against the AIDS virus.

Use them every time, from start to finish, according to the manufacturers' directions. Because no one has ever been cured of AIDS. More than 40,000 Americans have already died from it.

And even if you don't like condoms, using them is definitely better than that.

**HELP STOP AIDS. USE A CONDOM.**

AMERICAN FOUNDATION FOR AIDS RESEARCH

Ad Council — A Public Service of This Publication & The Advertising Council

NATIONAL AIDS NETWORK

Photo: Jerry Friedman

©1988, The Ad Council.

(Continued from Page 635)

PHYSICIANS WANTED

## PHOENIX, ARIZONA

A Neurologist is needed to join the prestigious Arizona Heart Institute in Phoenix, where currently there is one very busy Neurologist. Send CV to **Gordon Crawford, Manager, Professional Relations, Humana Inc., Dept HH-5, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.**

## The DEPARTMENT of PEDIATRIC HEMATOLOGY/ONCOLOGY at VALLEY CHILDREN'S HOSPITAL

is seeking a second, full-time hospital-based Pediatric Hematologist/Oncologist. The candidate must be BC or BE in Pediatric Hematology/Oncology. Responsibilities include patient care, teaching, and clinical research.

Valley Children's Hospital is affiliated with the Children's Cancer Study Group and with the University of California, San Francisco, Fresno Pediatric Residency Program.

Please contact:

**Stan Schofield**
**Assistant Vice President**
**Medical Affairs,**
**Valley Children's Hospital**
**3151 N. Millbrook**
**Fresno, CA 93703**

PHYSICIANS WANTED

## CALIFORNIA FAMILY PRACTICE

Internal Medicine, Surgeon, and Pediatric physicians to join Family Walk-In Medical Centers staff, a growing health care provider with five medical centers in Fresno, California, which is located in the Central San Joaquin Valley. Fresno metropolitan area has a population of over 400,000. Easy access to major metropolitan areas, Pacific coast and the Sierras. Salary guarantee of $100K to $120K for Family Practice, Internal Medicine, and Pediatric physicians; $150K for Surgeons, or equal to an average of the last two years' earnings, whichever is greater. Malpractice paid. Excellent working conditions. Contact **Juanita Perry, Human Resources Director, Family Walk-In Medical Centers, 1021 E. Herndon Ave, Fresno, CA 93710; (209) 449-6430**

**PEDIATRIC HEMATOLOGIST/ONCOLOGIST, BC/BE, LOS ANGELES.** Full-time at a private, nonprofit downtown university affiliated hospital and outpatient clinic for children with sickle-cell disease, hemophilia, malignancies of the musculoskeletal system, and other disorders. Remuneration starts at $110,000 (BE) to $120,000 (BC) with benefits and opportunities for advancement. Call every fourth night and fourth weekend for entire pediatric service. Renowned treatment team includes specialized nurses and social workers. Many indigent patients subsidized by a private foundation. Clinical research encouraged. Send CV to Carol K. Kasper, MD, 2400 S. Flower St, Los Angeles, CA 90007.

**BC/BE NORTHWESTERN CALIFORNIA.** OB/GYN needed to join the oldest office in the Redwood area on the North Coast. An excellent opportunity for a male or female, American trained physician. Excellent compensation and incentive program leading to corporate membership in one year. Three physicians in office but only two doing Obstetrics. Send CV and references to T. W. Loring, MD or W. C. Weiderman, MD, 2607 Harris St, Eureka, CA 95501; (707) 442-4593.

**INTERNAL MEDICINE,** northern California. BC/BE Internist to join four busy Internists in high quality practice on San Francisco Peninsula. Endocrinology or Rheumatology subspecialty welcomed. Reply to Number 202, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**SAN FRANCISCO NORTH BAY AREA/NAPA VALLEY.** Immediate openings (career and part-time) in a multidiscipline Emergency Department for physicians trained in Emergency Medicine, Internal Medicine, Family Practice, or Pediatrics. Full in-house multispecialty coverage. Complete generous benefit package. Contact Robert Mack, MD, Kaiser Hospital, 975 Sereno Dr, Dept WJM, Vallejo, CA 94589; (707) 648-6200. EOE.

POSITIONS AVAILABLE

## FAMILY NURSE PRACTITIONER

Three residency trained BC Family Practitioners seek a Family Nurse Practitioner to join their community health center practice. Located on the eastern slopes of the Sierras in northeastern California. Practice entails full scope of Family Practice. Excellent opportunity for recreation in local mountains including fishing, hiking, bicycling, camping, water-skiing, wind-surfing, sailing and in winter, both downhill and cross-country skiing. Includes a complete benefit package, malpractice coverage, health insurance, vacation, CME, etc. Salary commensurate with experience. Staff includes two Family Nurse Practitioners, one physician assistant, clinical psychologist, registered dietician, health educators, biofeedback therapist, and prenatal instructors. If interested send CV to **NRHC, Inc, 1306 Riverside Dr, Susanville, CA 96130, Attn: Paul W. Holmes, MD, Medical Director; or call (916) 257-7849**

**EMERGENCY MEDICAL SERVICES COORDINATOR.** $3,045 to $3,638 per month. Requires three years administrative experience in an Emergency Medical Services Program and possession of a Mobile Intensive Care Nurse (MICN) certificate. Excellent benefits. File application immediately with **Marin Co. Pers. Ofc., Rm. 423, Civic Center, San Rafael, CA 94903; (415) 499-6104. An EOE/AAE.**

PRACTICES AVAILABLE

**NORTHERN CALIFORNIA FAMILY PRACTICE.** Excellent starting or relocation opportunity. Experiencing good growth. Alpine setting. Four beautiful seasons. Collecting $192K. Asking price $38K. Reply to Number 206, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**FAMILY PHYSICIAN.** Active Family Practice for sale in W. Valley area of San Jose, California in a three physician association. Average 25 patients per day, four days per week. Call one to two nights, once every two weekends. Assistance available. Call Clark Anderson (408) 866-4028.

**SOUTHERN CALIFORNIA** inland empire. Fastest growing area in state. General practice 35 years, no OB. Good 325-bed hospital. Good exchange call group every sixth weekend. Will introduce. Terms: reply to Number 203, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**NORTHERN CALIFORNIA.** Urgent and Routine Care Clinic. Currently limited as a one physician operation. Large patient base. 2,600 square feet. Fully equipped and computerized. Collecting $265K. Country setting. Reply to Number 205, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

Ads Get Results!

CLASSIFIED INFORMATION
(415) 541-0900, Ext 376

(Continued on Page 638)

(Continued from Page 637)

## PRACTICES AVAILABLE

**NORTHERN AND CENTRAL CALIFORNIA**

Established practices available. Dermatology, Family, Internal Medicine, OB/GYN, Ophthalmology, Otolaryngology, Pediatrics, Plastic Surgery, and Urology. Reasonable terms and prices. Call/write **Bradshaw Associates, 21 Allamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.**

**FAMILY PRACTICE**—San Diego North County Inland. Gross $256,000. Mature quality practice with excellent patient base. Well located 2,000 square foot office. No Medi-Cal. Practice Consultants (619) 528-2321.

**CORONA, SOUTHERN CALIFORNIA.** Great opportunity to take over a busy established Internal Medical/Pulmonary Disease practice. Good coverage. Excellent income. Negotiable terms. Reply to Number 199, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**FAMILY PRACTICE AVAILABLE.** Large practice next to community hospital in Ogden, Utah. Established five years, new equipment, full computer system. Reply to Number 196, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**INTERNAL MEDICINE.** Practice available, Prescott, Arizona. A fine group of regular patients. Excellent living, facilities, coverage. Call for details (602) 445-2335 after 6 pm. Expanding territory.

**DERMATOLOGY OPPORTUNITIES IN CALIFORNIA.** Active, established practices available in San Francisco, Central Valley, and Sacramento areas. Contact Bradshaw Associates, 21 Altamount Dr, Orinda, CA 94563; (415) 376-0762.

**INTERNAL MEDICINE**—San Diego City, high development area. Gross $160,000. Low overhead with high net cash flow. Contact Practice Consultants. (619) 528-2321, Dr Bernard Press, Broker.

**INTERNAL MEDICINE OR FAMILY PRACTICE.** Beautiful Point Loma, San Diego, California. Well established solo Family Practitioner. Will introduce. Reliable call group. Great 250-bed hospital support. (619) 223-1666.

**BEAUTIFUL NAPA VALLEY, CALIFORNIA.** Solo Psychiatric practice. Good clientele. Potential for growth as desired. Physician retiring. Residence available. Call David Lucchesi, (707) 552-3831.

**SAN DIEGO COUNTY.** Cardiology, Internal, OB/GYN and Pediatric practices available. Long established—doctors retiring. Various prices and low down payments. Call CBI, San Diego County's professional practice sales specialists, (619) 283-7009.

**WELL ESTABLISHED GENERAL INTERNIST'S PRACTICE.** Excellent coverage and income. Silicon Valley. Physician will retire incrementally. U.S. trained BE/BC only, please. Reply to Number 178, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

## OFFICE SPACE

**GROWTH AREA OF SANTA CLARA VALLEY.** New medical office space for lease in the growth area of Silicon Valley, Morgan Hill, California. Easy access, abundant parking, well located, generous tenant improvement allowances. Excellent patient referral sources. Contact Dr Jon Hatakeyama, (408) 779-7391.

**SPACIOUS MEDICAL CLINIC** located in small Montana community known as Livingston, situated on the famed Yellowstone River, which is a blue ribbon trout stream. This area is a fly fisherman and hunter's paradise as we are only 52 miles from Yellowstone National Park. The clinic located across from the Livingston Memorial Hospital has 5,000 square feet on each of two floors and is set up for a complete medical clinic. Easy terms. Call (406) 494-3447.

## LOCUM TENENS

**WESTERN PHYSICIANS REGISTRY**
**Locum Tenens Service**
**Permanent Placement**

Since 1980, WPR has served the needs of California's physicians. When someone needs coverage or ongoing, part-time help, we find the right physician. When a practice must expand, we find a permanent associate. We pride ourselves on our discretion, our very personal service matching the right person with the right job. We work only in California, concentrating our efforts where we know our market. Our clients include private practices, HMOs, urgent care centers, emergency departments, multispecialty groups, and community clinics.

**Northern California**
**Carol Sweig and Jim Ellis, Directors**
**(415) 673-7676 or (800) 437-7676**

**Southern California**
**Tracy Zweig, Director**
**(818) 999-1050 or (800) 635-3175**

Your Access to Quality
Physicians and Practice Opportunities.
1-800-462-6573

LOCUM TENENS, INC.
A Division of Jackson and Coker
With offices in Atlanta and Denver
115 Perimeter Center Place
Suite 380-WJML0
Atlanta, GA 30346

**locum tenens:**
**"the interim solution"**

Why make a long-term commitment *before* you really want to? Until you're ready to "sign on the bottom line"... enjoy freedom, flexibility, and professional satisfaction as a PRN *locum tenens* physician. Call us toll-free for details.

The **PRN** Physicians
1-800-531-1122
Member Interim Physician Placement℠

## PLACEMENT SERVICES

**AT LAST!** Western Practitioner Resources places nurse practitioners, physician assistants, and certified nurse midwives in your clinical setting. Please phone Heidi Bourne, Director, (800) 345-5859 or (707) 839-5859.

## FINANCIAL SERVICES

**$5,000-$60,000 FOR PHYSICIANS.** Unsecured signature loans for any need including taxes, debts, investments, etc. No points or fees. Best rates. Level payments up to six years—no prepayment penalty. Call toll free 1 (800) 331-4952, Medi-Versal Department 114.

## REAL ESTATE

**RELOCATION, RETIREMENT, SPECULATION.** Lewiston, Idaho. Executive home for sale. Recently remodeled, excellent condition, 2,800 square feet. Five bedrooms with master suite, den, utility room, formal dining room, living room with fireplace, swimming pool on a private lot with river view. Sacrifice sale due to relocation. $120,000. Conact (208) 743-3531 days or (208) 746-5031 evenings.

**SOUTHERN CALIFORNIA.** Beautiful waterfront property in the Ventura keys. Custom home with boat dock, in a professional neighborhood. Adjacent to the Ventura harbor and marina. Call Jack Finnegan (805) 648-5915.

**CLASSIFIED INFORMATION**
**(415) 541-0900, Ext 376**

When you give blood you give another birthday, another laugh, another hug, another chance.

American Red Cross
Please give blood.
Ad Council

(Continued on Page 640)

# YOU CAN REACH THE GREEN FASTER WITH SCPIE'S NEW AGE 55 RETIREMENT PLAN

When the urge to escape grows strong, and you yearn for the relaxation you've earned, SCPIE's retirement plan can provide the reassurance you're looking for.

A SCPIE member who has been insured for five years immediately prior to retirement, and who quits practice completely and permanently, can retire at age 55 or thereafter with no "tail" cost.

Of course, that's only one advantage of joining an A+ rated, policyholder-owned insurance company. Many doctors join because they appreciate the other benefits which SCPIE offers.

For instance, SCPIE's policy provides broader coverage, giving you greater peace of mind than many other plans. As a doctor-owned company, we do not look for loopholes (exclusions) that save money but leave our members short-changed when it comes to protection.

Premiums are set by doctors on the SCPIE Board of Governors who pay those premiums themselves. They strive to hold costs as low as possible, while keeping SCPIE strong and solvent. If premiums turn out to be more than needed to pay claims and costs, the excess is returned.

SCPIE is on top of the leader board. It's worth a call to find out what we can do for your retirement game.

Sponsored by the Medical Associations and Societies of Kern, Los Angeles, Orange, Riverside, San Bernardino, San Luis Obispo, Santa Barbara and Ventura Counties. Available in other areas. Also sponsored by The California Association of Oral and Maxillofacial Surgeons.

**scpie**

**Southern California Physicians Insurance Exchange**

2029 Century Park East
Suite 2300
Los Angeles, CA 90067
(213) 552-8900 *(Collect)*
(619) 544-0163
*(In San Diego County)*

(Continued from Page 638)

COMPUTER INFORMATION

WANT TO TRACK YOUR PATIENTS ELECTRONICALLY?

Then INTELLITRACK is for you.
With The INTELLITRACK Software System You Can:

-Track Patient Diagnosis and Prescriptions
-Track Patient Visits
-Automate Patient Billing
-Generate Daily Accounting Reports, etc.

Call Now, Mention This Ad and Receive a Special Low Price

Intellicode Software Company
4755 Lyric Lane
San Jose, Ca. 95111
(408) 629 - 4086


## DON'T FORGET!

The deadline for submitting classifieds for the July issue of WJM is May 25. Send your advertisement to

**Classified Advertising**
**WJM, PO Box 7602**
**San Francisco, CA 94120-7602**

COURSES

### CRITICAL CARE CARDIOLOGY

August 2-4, 1990. San Francisco, California. Fees: $420 for ACC members; $490 for nonmembers; $315 for residents, fellows-in-training, nurses, and technicians. 16 Category 1 credit hours. For information, call **American College of Cardiology (800) 253-4636; in Maryland (301) 897-5400, ext 228.**

### TUTORIALS IN THE TETONS

August 27-29, 1990. Moran, Wyoming. Fees: $365 for members; $450 for nonmembers. 12 Category 1 credit hours. For information, call **American College of Cardiology (800) 253-4636; in Maryland (301) 897-5400, ext 226.**

COMPUTER INFORMATION


2V MEDTECH INTERNATIONAL CORP.

DIAGNOSIS 2V STAT TREATMENT

PRESENTS

2V STAT Medical Decision Support Software Covering 69 Specialties—Algorithms and Text

PLUS

COMPUTER 80286/12 MHz Turbo CPU 80 MB HD EGA Color Monitor Color Graphic Card 40 MB Back-up Drive and Printer

$5962
(for complete system)

ORDER NOW!
1•800•228•STAT
Technical Support Call 1•404•956•1855

2490 Windy Hill Road, Suite 201 • Marietta, Georgia 30067
Fax 404•956•7065 Telex 551341 MedVideo FastLink 6227779660


COURSES

**TITLE: KU SUMMER MEDICAL SYMPOSIUM MEDICINE FOR THE PRACTICING PHYSICIAN.** Date: July 19-22, 1990. Sponsor: The University of Kansas Medical Center. Location: Broadmoor Hotel and Convention Center, Colorado Springs, Colorado. Fee: $325. Credit: AMA Category I: 15 hours. Contact: Andrea Shaw, University of Kansas Medical Center, Office of Continuing Education, Rainbow and Olathe Blvds, Kansas City, KS 66103; (913) 588-4480.

Just a fraction of what we spend dining out could help pick up the tab for a good cause.

It's so easy to help your community, when you think about it.

Millions of people have helped make five percent of their incomes and five hours of volunteer time per week the standard of giving in America.

Get involved with the causes you care about and give five.

Give Five. What you get back is immeasurable

The Western Journal of Medicine

SINCE 1902 • CIRCULATION 56,000+

# Classified Advertisements

The rate for each insertion is **$7 per line** (average six words per line) **with five line ($35) minimum.** A confidential box number (in lieu of your address) can be assigned to your advertisement for $5 each month. The replies to the box number will be directly forwarded to you as they arrive at *WJM*'s office.

**Classified display rates $50 per inch. Maximum sizes: 1 column by 10 inches or 2 columns by 5 inches. Larger classified ad space by special arrangements.**

Copy for classified advertisements should be received not later than **25th of the second month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

**Please Type or Print Advertising Copy**

## Classified Advertisements Are Payable in Advance

THE WESTERN JOURNAL OF MEDICINE
P.O. BOX 7602, SAN FRANCISCO, CA 94120-7602
(415) 541-0900 EXT. 376

# ad copy

Print or Type Clearly

Number of lines _____ × $7 = $_____

Optional: Confidential box number charge: +$5 = _____

**Subtotal (minimum $35 *or* minimum $40 with confidential box number)** $_____

Number of insertions _____ × $_____ = (subtotal)

**Check enclosed for:** $_____

Name (Please Print)

Contact

Address

City/State/Zip

(_____)
Phone

Signature

## WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

**Alaska State Medical Association**—2401 E 42nd Ave, Suite 104, Anchorage 99508. (907) 562-2662. Annual Meeting: June 7-9, 1990, Alaska Land, Fairbanks.

**Arizona Medical Association, Inc**—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 7-9, 1990, Wyndham, Paradise Valley.

**California Medical Association**—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-8, 1991, Bally's Grand Hotel, Reno.

**Colorado Medical Society**—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 13-16, 1990, Keystone.

**Hawaii Medical Association**—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 12-14, 1990, Ilikai, Honolulu.

**Idaho Medical Association**—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 26-28, 1990, Sun Valley.

**Montana Medical Association**—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 4-6, 1990, Sheraton, Billings.

**Nevada State Medical Association**—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: June 21-23, 1990, Hyatt, Lake Tahoe.

**New Mexico Medical Society**—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 4-5, 1990, Albuquerque.

**Oregon Medical Association**—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1991, date and location to be announced.

**Utah Medical Association**—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 12-14, 1990, Marriott Hotel, Salt Lake City.

**Washington State Medical Association**—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 19-22, 1990, Sheraton, Spokane.

**Wyoming Medical Society**—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 14-16, 1990, Jackson Lake Lodge, Moran.

## ADVERTISING INDEX


BLUE CROSS OF CALIFORNIA . . . . . 495

BLUE SHIELD OF CALIFORNIA . . . . . 625

BURROUGHS WELLCOME
*Zovirax* . . . . . 481, 482

CLASSIFIED ADVERTISING . . . . . 628, 630, 632, 633, 634, 635, 637, 638, 640

CNA INSURANCE COMPANY . . . . . 475

THE DOCTORS' COMPANY . . . . . 623

ELI LILLY & COMPANY
*Axid* . . . . . 487, 627

GLAXO INC
*Zantac* . . . . . *3rd and 4th covers*

*HOFFMANN-LA ROCHE LABORATORIES*
*Librax* . . . . . 468, 469

INSURANCE CORPORATION OF AMERICA . . . . 488, 489

KAISER PERMANENTE . . . . . 631

THE MGIS COMPANIES . . . . . 467

MERCK SHARP & DOHME
*Vasotec* . . . . . 2nd cover, 465, 466

PALISADES PHARMACEUTICALS INC.
*Yocon* . . . . . 497

PARKE—DAVIS
*Lopid* . . . . . 477, 478

SIMMONDS . . . . . 471

SK&F LAB COMPANY
*Tagamet* . . . . . 497, 498

SOUTHERN CALIFORNIA PHYSICIANS INSURANCE EXCHANGE . . . . . 639

UNIVERSITY MICROFILM . . . . . 626

THE UPJOHN COMPANY
*Rogaine* . . . . . 472, 473, 474

US AIR FORCE . . . . . 629

US ARMY RESERVE . . . . . 633

VICOM . . . . . 471

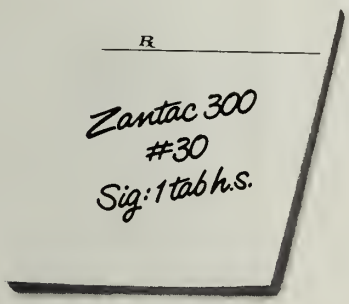
WELLS FARGO BANK . . . . . 491

THE WESTERN JOURNAL OF MEDICINE
*Addiction Medicine Order Form* . . . . . 492
*Special Issues* . . . . . 484
*Subscription* . . . . . 483, 636

*In active duodenal ulcers*

# Once-a-night h.s. therapy controls acid rain

**Zantac® 300**
*ranitidine HCl/Glaxo 300 mg tablets*




**ZANTAC® 150 Tablets**
**(ranitidine hydrochloride)**
**ZANTAC® 300 Tablets**
**(ranitidine hydrochloride)**

**BRIEF SUMMARY**

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

**INDICATIONS AND USAGE:** ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

**CONTRAINDICATIONS:** ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

**PRECAUTIONS: General:** 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

**Laboratory Tests:** False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

**Drug Interactions:** Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella*, *E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

**Pregnancy:** ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Nursing Mothers:** ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

**Pediatric Use:** Safety and effectiveness in children have not been established.

**Use in Elderly Patients:** Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

**ADVERSE REACTIONS:** The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

**Central Nervous System:** Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

**Cardiovascular:** Rare reports of tachycardia, bradycardia, and premature ventricular beats.

**Gastrointestinal:** Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

**Hepatic:** In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

**Musculoskeletal:** Rare reports of arthralgias.

**Hematologic:** Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

**Endocrine:** Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC® (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

**Integumentary:** Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

**Other:** Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

**OVERDOSAGE:** Information concerning possible overdosage and its treatment appears in the full prescribing information.

**DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer:** The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

**Maintenance Therapy:** The current recommended adult oral dosage is 150 mg at bedtime.

**Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome):** The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

**Benign Gastric Ulcer:** The current recommended adult oral dosage is 150 mg twice a day.

**GERD:** The current recommended adult oral dosage is 150 mg twice a day.

**Dosage Adjustment for Patients with Impaired Renal Function:** On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

**HOW SUPPLIED:** ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

**Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.**

August 1987

**Glaxo**

Glaxo Inc.
Research Triangle Park, NC 27709

©Copyright 1987, Glaxo Inc. All rights reserved.

# CONTROL ACID RAIN

**with once-a-night h.s. therapy for active duodenal ulcers**

**Zantac® 300**

ranitidine HCl/Glaxo 300 mg tablets

Glaxo ROCHE

See adjacent page for Brief Summary of Product Information

COUNTWAY LIBRARY 110212 WJM
OF MEDICINE
EXCHANGE OFFICE
10 SHATTUCK STREET
BOSTON, MA 02115-6011

ARIZONA MEDICINE
SI

DISPLAY SHELVES

# The Western Journal of Medicine

VOLUME 152 • NUMBER 6 JUNE 1990


**CLINICAL INVESTIGATION**

677 Misdiagnosing Ventricular Tachycardia in Patients With Underlying Conduction Disease and Similar Sinus and Tachycardia Morphologies
B D HALPERIN, J KRON, J E CUTLER, P J KUDENCHUK, and J H McANULTY

**CLINICAL MEDICINE**

683 Parenteral Nutrition Use at a University Hospital—Factors Associated With Inappropriate Use
S J KATZ and R K OYE

**MEDICAL PROGRESS**

687 Current Status of Renal Transplantation
M G SURANYI and B M HALL

**MEDICAL STAFF CONFERENCE**

697 High-Dose Epinephrine Therapy and Other Advances in Treating Cardiac Arrest
Discussant: M L CALLAHAM

**EPITOMES**

704 Important Advances in Nuclear Medicine

**EDITORIALS**

711 Medicine in Extraordinary Times • Kidney Transplant Revisited (1990)

**CASE REPORTS**

714 Acute Pancreatitis Associated With High-Dose Interleukin-2 Immunotherapy for Malignant Melanoma
G R BIRCHFIELD, J H WARD, B G REDMAN, L FLAHERTY, and W E SAMLOWSKI

716 Rhabdomyolysis and *Staphylococcus aureus* Septicemia in a Man With the Acquired Immunodeficiency Syndrome
A W WU, K BENIRSCHKE, and J A McCUTCHAN

719 Capgras's Syndrome Associated With Sensory Loss
S F SIGNER, P C VAN NESS, and R J DAVIS

**CORRESPONDENCE**

721 Patients' Presence in Prenatal Screening • *Blastocystis hominis* • Espresso Maker's Wrist • A Pathologist's View of Mohs' Micrographic Surgery • Ruminations of an Aspiring Californian • Putting Practice Into Law • Zinc • Confidential and Anonymous Testing

**HEALTH CARE DELIVERY**

725 Low-Birth-Weight Effects of Demographic and Socioeconomic Variables and Prenatal Care in Pima County, Arizona
I L SCHWARTZ

**MEDICINE IN PERSPECTIVE**

729 Trench Foot—A Study in Military Medical Responsiveness in the Great War, 1914-1918
J S HALLER, Jr

**SPECIAL EDITORIALS**

734 A Tribute to MSMW
D L WILBUR
L H SMITH, Jr
L H CLEVER

**OTHER FEATURES**

653 Subscription Information

664 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

738 Volume Index

747 Classified Advertising

756 Western State Medical Associations' Meetings

**Detailed Table of Contents:** 654, 658, 662


THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE BOSTON, MA
JUN 26 1990

Official Journal of the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology

# THERAPY THAT MAY BE AS SILENT AS HYPERTENSION ITSELF

VASOTEC® (Enalapril Maleate, MSD) is generally well tolerated and not characterized by certain undesirable effects associated with selected agents in other antihypertensive classes.

VASOTEC is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

A diminished antihypertensive effect toward the end of the dosing interval can occur in some patients.

For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

Copyright © 1989 by Merck & Co., Inc.

FOR MANY HYPERTENSIVE PATIENTS
ONCE-A-DAY
VASOTEC®
(ENALAPRIL MALEATE | MSD)

# VASOTEC®

## (ENALAPRIL MALEATE | MSD)

VASOTEC is available in 2.5-mg, 5-mg, 10-mg, and 20-mg tablet strengths.

**Contraindications:** VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

**Warnings:** *Angioedema.* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

*Hypotension.* Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Patients with heart failure given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

*Neutropenia/Agranulocytosis:* Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

**Precautions:** *General: Impaired Renal Function.* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

**Evaluation of patients with hypertension or heart failure should always include assessment of renal function.** (See DOSAGE AND ADMINISTRATION.)

*Hyperkalemia.* Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions.*)

*Surgery/Anesthesia:* In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

*Information for Patients:*

*Angioedema:* Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

*Hypotension.* Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure, patients should be advised to consult with the physician.

*Hyperkalemia:* Patients should be told not to use salt substitutes containing potassium without consulting their physician.

*Neutropenia.* Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

*Drug Interactions.*

*Hypotension. Patients on Diuretic Therapy.* Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

*Agents Causing Renin Release.* The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

*Other Cardiovascular Agents:* VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

*Agents Increasing Serum Potassium:* VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

*Lithium:* Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

*Pregnancy–Category C.* There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies of enalapril in pregnant women. However, data are available that show enalapril crosses the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined, VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity.

*Nursing Mothers:* Milk in lactating rats contains radioactivity following administration of $^{14}C$ enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

*Pediatric Use:* Safety and effectiveness in children have not been established.

**Adverse Reactions:** VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

*HYPERTENSION:* The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

*HEART FAILURE:* The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

*Cardiovascular.* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances, atrial fibrillation, palpitation.

*Digestive:* Ileus, pancreatitis, hepatitis (hepatocellular or cholestatic jaundice), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.

*Musculoskeletal:* Muscle cramps.

*Nervous/Psychiatric.* Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

*Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

*Respiratory:* Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection.

*Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, hyperhidrosis.

*Special Senses:* Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgias/arthritis, myalgias, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash, and other dermatologic manifestations.

*Angioedema:* Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

*Hypotension:* In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.3% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

*Clinical Laboratory Test Findings:*

*Serum Electrolytes:* Hyperkalemia (see PRECAUTIONS), hyponatremia.

*Creatinine, Blood Urea Nitrogen:* In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

*Hemoglobin and Hematocrit:* Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

*Other (Causal Relationship Unknown):* In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported. A few cases of hemolysis have been reported in patients with G6PD deficiency.

*Liver Function Tests:* Elevations of liver enzymes and/or serum bilirubin have occurred.

**Dosage and Administration:** *Hypertension:* In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

*Dosage Adjustment in Hypertensive Patients with Renal Impairment.* The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

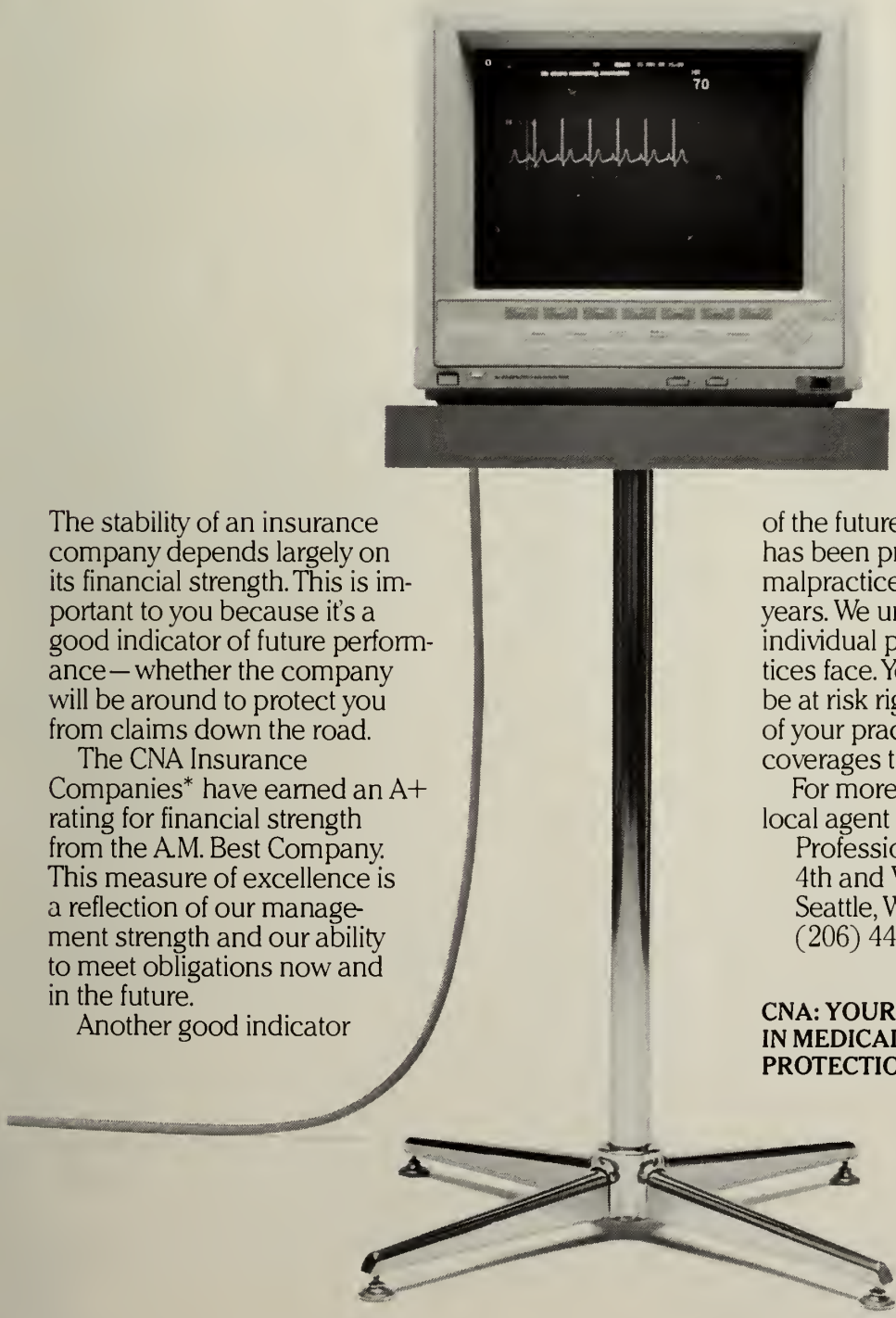
*Heart Failure:* VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects.*) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

*Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia:* In patients with heart failure who have hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine >1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, *Heart Failure,* WARNINGS, and PRECAUTIONS, *Drug Interactions.*) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

*For more detailed information, consult your MSD Representative or see Prescribing Information, Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.* J9VS54R3(819)

MSD
MERCK SHARP & DOHME

# CNA's financial stability can be vital to the health of your practice.



The stability of an insurance company depends largely on its financial strength. This is important to you because it's a good indicator of future performance—whether the company will be around to protect you from claims down the road.

The CNA Insurance Companies* have earned an A+ rating for financial strength from the A.M. Best Company. This measure of excellence is a reflection of our management strength and our ability to meet obligations now and in the future.

Another good indicator of the future is past performance. CNA has been protecting doctors against malpractice claims for more than 20 years. We understand the special risks individual physicians and group practices face. Your personal assets could be at risk right along with the assets of your practice, and we can tailor coverages to meet your exact needs.

For more information, contact your local agent or:

Professional Insurance Corporation
4th and Vine Bldg.-Suite 200
Seattle, WA 98121
(206) 441-7960

**CNA: YOUR PARTNER IN MEDICAL MALPRACTICE PROTECTION**

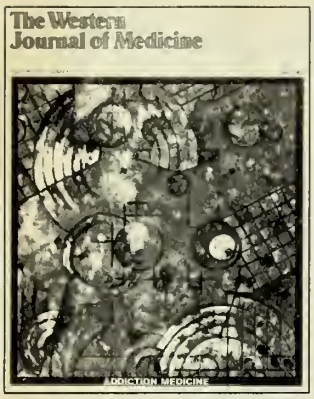
*The CNA Physicians Protection Program is underwritten by Continental Casualty Company, one of the CNA Insurance Companies.

**CNA**

**For All the Commitments You Make®**

# SPECIAL ISSUES

THE WESTERN JOURNAL OF MEDICINE Special May Issue:

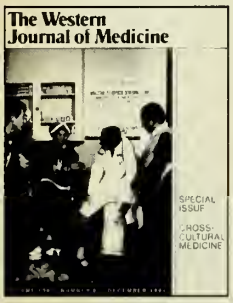



MAY 1990

## Addiction Medicine and the Primary Care Physician

- OVERVIEW OF ADDICTION MEDICINE *David Smith, Editor/Founder, Haight-Ashbury Free Clinic*
- CHEMICAL DEPENDENCE AND THE WORK PLACE *John Osterloh and Charles Becker*
- THE DISEASE CONCEPT OF ALCOHOLISM *John Wallace*
- COGNITIVE IMPAIRMENTS IN RECOVERING ALCOHOLICS *George Fein*
- SUBSTANCE ABUSE AND PULMONARY PATHOLOGY *Donald Tashkin*
- SPECIAL POPULATIONS: THE ADOLESCENT *Martha Morrison*
- METHADONE MAINTENANCE IN THE TREATMENT OF OPIOID DEPENDENCE *Joan Zweben*
- TREATMENT OF NICOTINE DEPENDENCE IN THE CHEMICALLY DEPENDENT PATIENT *Karen Sees*
- PHARMACOLOGIC APPROACHES TO THE TREATMENT OF COCAINE DEPENDENCE *Wanda A. Taylor and Mark S. Gold*

## Cross-cultural Medicine

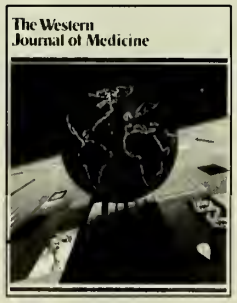



Cross-cultural medicine is devoted to the care of patients of different, cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983. 2nd reprinted edition.

## Women and Medicine

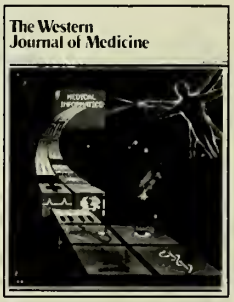
This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients. Topics covered include liver disease, women and AIDS, heart disease, hysterectomy, PMS, ovarian cancer, and women physicians and organized medicine. Linda Hawes Clever, MD, Special Issue Editor, 1988.

## AIDS— A Global Perspective



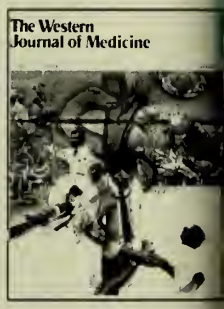

This issue, from the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent. Jonathan M. Mann, MD, Special Issue Editor, 1987.

## Medical Informatics




*Medical Informatics* explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

## High-Tech Medicine




This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

---

| Quantity | Per Copy* |
|---|---|
| Single copy | $5.00 |
| 2 to 10 | 4.00 |
| 11 to 50 | 3.50 |
| More than 50 | 3.00 |
| Cross-cultural | 7.50 |
| 50 copies or more | 6.50 |

*Note: USA/Canada postage and handling included, all other countries please add US $4.23 Air Printed Matter postage. Please add California and local sales tax where applicable.

## ORDER FORM

WJM 6

Name _____

Address _____ City/State/Zip _____

Charge my account: ☐ VISA ☐ MASTERCARD

# _____ Exp. date _____

Signature _____

Mail to: Circulation Department, The Western Journal of Medicine
P.O. Box 7602, San Francisco, CA 94120-7602

**Please send me:**

____copies of Addiction Medicine and the Primary Care Physician

____copies of Cross-cultural Medicine

____copies of Women and Medicine

____copies of AIDS—A Global Perspective

____copies of High-Tech Medicine

____copies of Medical Informatics

Payment must accompany order. Total amount enclosed $_____

# SEVEN WAYS TO SHARPEN YOUR MEDICAL SKILLS.

The Army Reserve offers a number of highly specialized medical courses you can't always get in civilian hospitals—with the kind of flexibility your busy schedule demands. Here is just a sampling of the unique training programs available to you in the Army Reserve:

COMBAT CASUALTY CARE Prepares you for treating trauma patients in your civilian career. Learn how to live, survive, and function in challenging environments.

ADVANCED TRAUMA/LIFE SUPPORT Teaches you how to treat trauma patients during the critical first hour of injury. Sponsored by the American College of Surgeons.

ADVANCED BURN LIFE SUPPORT Teaches you how to treat and manage the unique characteristics of the burn patient. Sponsored by the American Burn Association.

ADVANCED CARDIAC LIFE SUPPORT Centers upon the treatment and life-saving intervention associated with the acute cardiac patient. Sponsored by the American Heart Association.

TROPICAL MEDICINE Provides you with advanced in-depth training in parasitology, infectious diseases occurring in tropical and other areas of the world, and other related topics.

FLIGHT SURGEON Gives you a working knowledge of aviation medicine in a course that offers opportunities for frequent operational flights.

AVIATION MEDICINE Offers you a follow-up to the Flight Surgeon course and includes air ambulance operations, airfield operations, and aeromedical research.

Join a local medical unit and serve as few as 16 hours a month and 14 days of active duty during the year. The time you serve can be scheduled around your busy private practice.

You might also have the opportunity to participate in our Individual Mobilization Augmentee Program and serve just two weeks each year.

If you would like more information about these or other medical opportunities, or would like to be contacted by an Army Reserve physician, call 1-800-USA-ARMY.

**ARMY RESERVE MEDICINE. BE ALL YOU CAN BE.®**

# The Western Journal of Medicine

SINCE 1902 ISSN 0093-0415

PO BOX 7602 • SAN FRANCISCO, CALIFORNIA 94120-7602 • TELEPHONE (415) 541-0900



LINDA HAWES CLEVER, MD, *Editor*
LLOYD H. SMITH, Jr, MD, *Associate Editor*
DIANA L. McANINCH, *Managing Editor*
SALLY LINEBARGER, *Assistant Meneging Editor*
SANDRA WILLETT, *Editorial Assistant*
JANICE ANDERSEN, *Senior Copy Editor*
FRITZ C. HEATON, *Advertising and Promotion Maneger*
NILA J. NICHOLS, *Circuletion Coordinetor*
DOROTHY A. HEARST, *Classified Advertising*

editorial communications to DR CLEVER • business communications to MS McANINCH



Official Journal of the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.



## EDITORIAL BOARD

*Editor Emeritus*
Malcolm S. M. Watts, San Francisco, Calif

*Editor Emeritus*
Dwight L. Wilbur, San Francisco, Calif

*Editor for Clinical Investigation*
Kenneth D. Gardner, Jr, Albuquerque, NM

*Special Editor for Arizona*
Marshall B. Block, Phoenix, Ariz

*Special Editor for Denver*
David Shander, Denver, Colo

*Special Editor for Idaho*
E. R. W. Fox, Coeur d'Alene, Idaho

*Special Editor for Nevada*
Anton P. Sohn, Reno, Nev

*Special Editor for New Mexico*
I. Brian Taylor, Carlsbad, NM

*Special Editor for Uteh*
John H. Holbrook, Salt Lake City, Utah

*Speciel Editor for Washington*
David Hopkins, Federal Way, Wash

*Special Editor for Wyoming*
Joseph P. Murphy, Casper, Wyo

*Allergy*
Merle S. Scherr, Scottsdale, Ariz

*Anesthesiology*
Ronald D. Miller, San Francisco, Calif

*Biostatistics and Epidemiology*
Virginia L. Ernster, San Francisco, Calif

*Cardiac and Thoracic Surgery*
Norman E. Shumway, Stanford, Calif

*Chest Diseases*
Leonard D. Hudson, Seattle, Wash
Thomas L. Petty, Denver, Colo

*Dermatology*
Clark Huff, Denver, Colo
Frank Parker, Portland, Ore
Gerald D. Weinstein, Irvine, Calif

*Emergency Medicine*
William A. Boehm, Alamogordo, NM
W. Richard Bukata, Flintridge, Calif
Clark Chipman, Portland, Ore
Thomas Elmendorf, Davis, Calif

*General end Femily Practice*
Charles W. Huff, Casper, Wyo
Norman Kahn, Sacramento, Calif
J. Jerome Wildgen, Kalispell, Mont

*Internal Medicine*
Philip R. Alper, Burlingame, Calif
Robert W. Burroughs, Spokane, Wash
Patricia Gabow, Denver, Colo
Harry R. Kimball, Boston, Mass
Darwin Palmer, Albuquerque, NM
George A. Porter, Portland, Ore
Irwin J. Schatz, Honolulu, Hawaii
Stephen I. Wasserman, San Diego, Calif
Laurens P. White, San Francisco, Calif

*Neurology*
J. Richard Baringer, Salt Lake City, Utah
Don F. Seelinger, Albuquerque, NM
W. C. Wiederholt, La Jolla, Calif

*Neurosurgery*
George A. Ojemann, Seattle, Wash
Robert F. Spetzler, Phoenix, Ariz
Charles B. Wilson, San Francisco, Calif

*Nuclear Medicine*
Philip Matin, Roseville, Calif

*Obstetrics and Gynecology*
Daniel Mishell, Jr, Los Angeles, Calif
Morton A. Stenchever, Seattle, Wash

*Occupational Medicine*
Linda Rosenstock, Seattle, Wash

*Ophthalmology*
John L. Keltner, Davis, Calif
Bruce E. Spivey, San Francisco, Calif

*Orthopedics*
George E. Omer, Albuquerque, NM

*Otolaryngology*
Paul H. Ward, Los Angeles, Calif

*Pathology*
Roy I. Davis, Phoenix, Ariz

*Pediatrics*
Roberta A. Ballard, San Francisco, Calif
Allen W. Mathies, Jr, Pasadena, Calif
William O. Robertson, Seattle, Wash

*Pharmacology*
Rubin Bressler, Tucson, Ariz

*Physical Medicine and Rehabilitation*
Julie G. Madorsky, Pomona, Calif

*Plastic Surgery*
Richard P. Jobe, Los Altos, Calif
Henry K. Kawamoto, Jr, Santa Monica, Calif

*Preventive Medicine and Public Health*
Joseph L. Lyon, Salt Lake City, Utah
Jonathan Mann, Geneva, Switz

*Psychiatry*
Ralph Crawshaw, Portland, Ore
Alan I. Levenson, Tucson, Ariz
R. Bruce Sloane, Los Angeles, Calif

*Radiology*
Gary Glazer, Stanford, Calif
Michael L. Manco-Johnson, Denver, Colo
Albert A. Moss, Seattle, Wash

*Surgery*
Haile T. Debas, San Francisco, Calif
Alex G. Little, Las Vegas, Nev
Frank G. Moody, Houston, Tex

*Urology*
Paul H. Lange, Seattle, Wash

*Senior Member at Large*
Edgar Wayburn, San Francisco, Calif

## ADVISORY BOARD, CLINICAL INVESTIGATION

George D. Molnar, Univ of Alberta
Murray A. Katz, Univ of Arizona
Ross E. Petty, Univ of British Columbia
Eldon Shaffer, Univ of Calgary
M. Eric Gershwin, Univ of California, Davis
Jacob Katz, Univ of California, Irvine
Delbert A. Fisher, Univ of California, Los Angeles
Kenneth M. Moser, Univ of California, San Diego
H. Benfer Kaltreider, Univ of California, San Francisco
Alan S. Nies, Univ of Colorado
Irwin J. Schatz, Univ of Hawaii
John Peacock, Univ of Nevada
Sanford Schneider, Loma Linda Univ
Kenneth D. Gardner, Jr, Univ of New Mexico
J. David Bristow, Univ of Oregon
Robert M. McAllister, Univ of Southern California
R. Marvin Bala, Univ of Saskatchewan
Allen D. Cooper, Stanford Univ
Gerald Rothstein, Univ of Utah
David R. Saunders, Univ of Washington



## ADVERTISING INFORMATION

Advertising Sales Representatives

EAST/MIDWEST: Cunningham Associates, James C. Cunningham and James Pattis, PO Box 308, Park Ridge, NJ 07656 • (201)767-4170/FAX (201) 767-8065

WEST: Lynne Jeffes, 10 Acacia Lane, Redwood City, CA 94062 • (415) 368-1898

CLASSIFIED: PO Box 7602, San Francisco, CA 94120-7602; overnight mail, 221 Main St, San Francisco, CA 94105 • Tel: (415) 541-0900, ext. 376

*Advertisements*—The journal is published the first week of the month. Advertising copy must be received no later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee. *The journal reserves the right to reject any advertisement.*


## SUBSCRIPTION INFORMATION

The subscription price per year is $30 in the United States and Canada (US funds); $50 in all other countries. Single copies are $5.00. USA/CANADA postage and handling included. All other countries add US $4.23 Air Printed Matter Postage. Address all subscription communications to:

THE WESTERN JOURNAL OF MEDICINE Circulation, PO Box 7602
San Francisco, CA 94120-7602 • Tel: (415) 882-5179

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $5.00 is applicable for each issue available.

*Change of Address*—Requests for change of address should give both the old and new address. Allow six weeks for changeover.

## SUBMITTING MANUSCRIPTS

Manuscripts for consideration should be sent to the editor, Linda Hawes Clever, MD, PO Box 7602, San Francisco, CA 94120-7602; overnight mail, 221 Main St, San Francisco, CA 94105.

*"Information for Authors"*—A complete guide to manuscript submission and *WJM* style appears in the January and July issues. Manuscripts may be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (*Annals of Internal Medicine*, Feb 1988; *The Medical Journal of Australia*, Feb 1988).

*Author Responsibility*—Authors are responsible for all statements, conclusions and methods of presenting subjects. Articles are accepted on condition that they are contributed solely to this journal.

*Manuscripts*—Ordinarily manuscripts should not exceed 3,000 words (less than 15 typed double-spaced pages). The *original* manuscript and two copies should be submitted, typed double-spaced throughout. If photographic illustrations are desired, three sets of clear, unmounted black and white glossy prints should be supplied. For line drawings, original artwork or glossy prints are acceptable. Tables should be typed on separate sheets of paper.

*Clinical Investigation*—Papers that authors wish considered for the Clinical Investigation section should be so designated in the transmittal letter. Such papers should describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease.

## PUBLISHER


Copyright 1990 by the California Medical Association • Owned and Published by the California Medical Association.

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with January and July.



***The Western Journal of Medicine***

(ISSN 0093-0415/USPS 084 480) is published monthly for $30 per year (USA and Canada) by the California Medical Association, 221 Main Street, San Francisco, CA 94105. Second-class postage paid at San Francisco and additional mailing offices.

**POSTMASTER:** Send address changes to *The Western Journal of Medicine*, Circulation, PO Box 7602, San Francisco, CA 94120-7602.

# TAKE A CLOSER LOOK

*at MGMA's Professional Liability Program...it may just expand your group's coverage and lower your cost.*

- Combined purchasing power of participating MGMA member groups.
- A.M. Best A+ (Superior) rated carriers.
- Exclusive to qualified MGMA member groups.
- Prior Acts coverage.
- Flexible limits of liability.
- Retrospective dividends.
- No cost reporting endorsement for disability or death.
- No cost reporting endorsement after 5 years and age 55.
- Other exclusive reporting endorsement benefits.

For more than 20 years, thousands of MGMA member groups have been provided with sound employee benefit insurance plans through The MGIS Companies. Now may be a good time for you to find out more about medical-professional liability plans offered exclusively to MGMA member groups.

Dividends are not guaranteed. Not all features available in all States.

*National Program Manager:*
**MGIS Property & Casualty Insurance Services, Inc.**
85 Great Oaks Boulevard, San Jose, CA 95119
Post Office Box 23400, San Jose, CA 95153-5351
408-365-3799 Toll Free: 800-969-MGIS Fax: 408-226-0271

# Investigators' evaluations confirm hair growth in male pattern baldness of the vertex

ROGAINE® Topical Solution (minoxidil 2%) is the *first* prescription medication proved effective for male pattern baldness of the vertex. The effect on frontal baldness has not been adequately studied.

Evidence of growth was demonstrated by physician evaluations of 1,431 patients in 27 centers across the United States. Patients were placed on ROGAINE or placebo and evaluated each month for four months. Response was judged to be no growth, new vellus (baby) hair, or minimal, moderate, or dense growth.

In addition, after the placebo group was discontinued, continuous application of ROGAINE over an additional eight months was evaluated to determine if nonvellus growth could be sustained.

START OF STUDY

START OF STUDY

START OF STUDY

Examples of minimal, moderate, and dense growth as evaluated by investigators

© 1989 The Upjohn Company

MINIMAL GROWTH

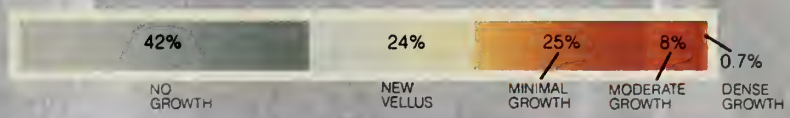
MODERATE GROWTH

DENSE GROWTH

*Four-Month Phase*

At the end of four months, 34% of 714 patients treated with ROGAINE were evaluated as showing minimal, moderate, or dense growth, while 20% of 717 patients showed minimal, moderate, or dense growth with placebo, a highly significant difference ($P<.0005$).

**Rogaine** (714)

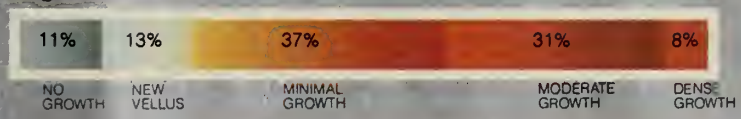



**Placebo** (717)

*Non-Placebo-Controlled Continuation Phase*

After 12 months, dense growth was observed in 8% of the 619 patients treated with ROGAINE, moderate growth in 31%, and minimal growth in 37%. Approximately one fourth of patients showed only vellus hair growth or no growth.

**Rogaine** (619)




*Compliance is Essential*

The multicenter studies indicate that a period of *four months or longer* of daily b.i.d. applications of ROGAINE is usually necessary before evidence of hair growth is apparent. Hair growth continued to increase in study subjects over months 5 through 12.

Continuous use is necessary to maintain hair growth. Newly grown hair returns to the untreated state three to four months after cessation of therapy with ROGAINE.

*Please see last page for brief summary of prescribing information.*

# Rogaine®

TOPICAL SOLUTION

minoxidil 2%

**Upjohn**

The Upjohn Company
Kalamazoo, MI 49001 USA

# Rogaine® Rx

TOPICAL SOLUTION minoxidil 2%

**INDICATIONS AND USAGE**
Male pattern baldness (alopecia androgenetica) of the vertex of the scalp. No effect has been seen on frontal baldness. At least four months of treatment are generally required before evidence of hair growth can be expected, further growth continues through one year. The new growth is not permanent; cessation of treatment will lead to its loss in a few months.

**CONTRAINDICATIONS**
Hypersensitivity to minoxidil, propylene glycol or ethanol.

**WARNINGS**
*1. Need for normal scalp.* Before starting treatment, make sure that the patient has a normal, healthy scalp. Local abrasion or dermatitis may increase absorption and hence the risk of side effects.
*2. Potential adverse effects.* Although extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects, greater absorption due to misuse, individual variability or unusual sensitivity could, at least theoretically, produce a systemic effect.
Experience with oral minoxidil has shown the following major cardiovascular effects (Review the package insert for LONITEN® Tablets for details):
—salt and water retention, generalized and local edema
—pericardial effusion, pericarditis, tamponade
—tachycardia
—increased incidence of angina or new onset of angina
Patients with underlying heart disease, including coronary artery disease and congestive heart failure, would be at particular risk of these potential effects. Additive effects could also emerge in patients being treated for hypertension.
Potential patients should have a history and physical, should be advised of potential risks and a risk/benefit decision should be made. Heart patients should realize that adverse effects may be especially serious. Alert patients to the possibility of tachycardia and fluid retention, and monitor for increased heart rate, weight gain or other systemic effects.

**PRECAUTIONS**
*General Precautions:* Monitor patients one month after starting ROGAINE and at least every six months afterward. Discontinue ROGAINE if systemic effects occur. The alcohol base will burn and irritate the eye. If ROGAINE reaches sensitive surfaces (eg, eye, abraded skin and mucous membranes) bathe with copious cool water.
Avoid inhaling the spray.
Do not use in conjunction with other topical agents such as corticosteroids, retinoids and petrolatum or agents that enhance percutaneous absorption. ROGAINE is for topical use only. Each mL contains 20 mg minoxidil and accidental ingestion could cause adverse systemic effects.
Decreased integrity of the epidermal barrier caused by inflammation or disease of the skin, eg, excoriations, psoriasis or severe sunburn, may increase minoxidil absorption.
*Patient Information:* A patient information leaflet is included with each package and in the full product information.
*Drug Interactions:* No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine.
*Carcinogenesis, Mutagenesis and Impairment of Fertility:* No carcinogenicity was found with topical application. Oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice. In rats, there was a dose-dependent reduction in conception rate.
*Pregnancy Category C:* ROGAINE should not be used by pregnant women.
*Labor and Delivery:* The effects are not known.
*Nursing Mothers:* ROGAINE should not be administered.
*Pediatric Use.* Safety and effectiveness have not been established under age 18.

**ADVERSE REACTIONS**
ROGAINE was used by 3510 patients in placebo-controlled trials. Except for dermatologic events, no individual reaction or reactions grouped by body systems appeared to be increased in the minoxidil-treated patients.
**Respiratory** (bronchitis, upper respiratory infection, sinusitis) 5.95%; **Dermatologic** (irritant or allergic contact dermatitis) 5.27%; **Gastrointestinal** (diarrhea, nausea, vomiting) 3.42%; **Neurology** (headache, dizziness, faintness, light-headedness) 2.56%; **Musculoskeletal** (fractures, back pain, tendinitis) 2.17%; **Cardiovascular** (edema, chest pain, blood pressure increases/decreases, palpitation, pulse rate increases/decreases) 1.28%; **Allergy** (non-specific allergic reactions, hives, allergic rhinitis, facial swelling and sensitivity) 1.03%; **Special Senses** (conjunctivitis, ear infections, vertigo) 0.94%; **Metabolic-Nutritional** (edema, weight gain) 0.60%; **Urinary Tract** (urinary tract infections, renal calculi, urethritis) 0.46%; **Genital Tract** (prostatitis, epididymitis) 0.46%; **Psychiatric** (anxiety, depression, fatigue) 0.28%; **Hematology** (lymphadenopathy, thrombocytopenia) 0.23%; **Endocrine** 0.09%.
Patients have been followed for up to 5 years and there has been no change in incidence or severity of reported reactions. Additional events reported since marketing include: eczema, hypertrichosis, local erythema, pruritus, dry skin/scalp flaking, sexual dysfunction, visual disturbances including decreased visual acuity, exacerbation of hair loss, alopecia.

**DOSAGE AND ADMINISTRATION**
Hair and scalp should be dry before application. 1 mL should be applied to the total affected areas twice daily. Total daily dose should not exceed 2 mL. If the fingertips are used to facilitate drug application, wash the hands afterwards.

**HOW SUPPLIED**
60 mL bottle with multiple applicators NDC 0009-3367-05
Caution: Federal law prohibits dispensing without a prescription.

B-1-S

**Upjohn**
The Upjohn Company
Kalamazoo, MI 49001 USA

© 1989 The Upjohn Company June 1989 J-9909



*The Western Journal of Medicine*

(ISSN 0093-0415/USPS 084 480) is published monthly for $30 per year (USA and Canada) by the California Medical Association, 221 Main Street, San Francisco, CA 94105. Second-class postage paid at San Francisco, CA and additional mailing offices.

**POSTMASTER:**
Send address changes to
*The Western Journal of Medicine*
Circulation, P.O. Box 7602
San Francisco, CA 94120-7602



# *Moving?*

Please give us six weeks notice and supply your personal reference number.

ID No.

302703 XX

The Western Journal of Medicine
P.O. Box 7602
San Francisco, CA 94120-7602

**The Western Journal of Medicine**

P.O. Box 7602
San Francisco, CA 94120-7602

# Be Sure To Get Your Own Copy.

## Return This Coupon.

WJ6/90

Enclosed is $_____ to cover _____subscriptions.

Subscription renewal ☐ Regular subscription ☐

Foreign subscription ☐ Bill me ☐

Student ☐ Resident ☐

TO:_____

Street _____

City/State/Zip _____

Specialty (If applicable) _____

Student/Resident Completion Date (Year) _____

Charge my account ☐ VISA ☐ MASTERCARD

#_____ Exp. date _____

Signature _____

**The Western Journal of Medicine**

If you are not using a credit card, please mail this coupon with enclosed payment to:

**Circulation Department**
P.O. Box 7602, San Francisco, California 94120-7602

Subscriptions, 12 issues per year
U.S. and Canada $30 1 year, $50 2 years

All other countries $50 1 year, $90 2 years
Student/Resident (USA and Canada): $15 per year

The Western Journal of Medicine

VOLUME 152 • NUMBER 6 • JUNE 1990

# CONTENTS


## CLINICAL INVESTIGATION

677 **Misdiagnosing Ventricular Tachycardia in Patients With Underlying Conduction Disease and Similar Sinus and Tachycardia Morphologies**
BLAIR D. HALPERIN, MD; JACK KRON, MD; JOEL E. CUTLER, MD; PETER J. KUDENCHUK, MD; and JOHN H. McANULTY
*From the Department of Medicine, Division of Cardiology, University of Colorado Health Sciences Center, Denver; the Department of Medicine, Division of Cardiology, Oregon Health Sciences University School of Medicine, Portland; and the Division of Cardiology, Harborview Medical Center, Seattle.*

## CLINICAL MEDICINE

683 **Parenteral Nutrition Use at a University Hospital—Factors Associated With Inappropriate Use**
STEVEN J. KATZ, MD, and ROBERT K. OYE, MD
*From the Robert Wood Johnson Clinical Scholars Program, University of Washington School of Medicine, Seattle, and the Department of Medicine, University of California, Los Angeles, School of Medicine.*

## MEDICAL PROGRESS

687 **Current Status of Renal Transplantation**
MICHAEL G. SURANYI, MBBS, FRACP, and BRUCE M. HALL, MBBS, FRACP, PhD
*From the Department of Medicine, Division of Nephrology, Stanford University Medical Center, Stanford, California.*

## MEDICAL STAFF CONFERENCE

697 **High-Dose Epinephrine Therapy and Other Advances in Treating Cardiac Arrest**
Discussant: MICHAEL L. CALLAHAM, MD
*A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco, School of Medicine. Taken from a transcription, it was prepared by Homer A. Bousey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.*

## EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

**Nuclear Medicine**
*Items of progress in nuclear medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance.*

704 **Single-Photon-Emission Computed Tomographic Imaging of the Bone**
ANDREW S. KLONECKE, MD, and I. ROSS McDOUGALL, MB, ChB, PhD


*(Continued on Page 658)*

ler anxiolytic
s working—
ut she's alert,
unctioning, and
t no risk of a
enzodiazepine
vithdrawal
yndrome when
herapy ends.

## BuSpar relieves anxiety and returns your patient to normal activity

...with no more sedation (10%) than induced by placebo (9%)[1]
...without inducing significant cognitive[2] or functional impairment*
...without producing a benzodiazepine withdrawal syndrome[3] upon discontinuation

*Effective choice for anxiety*

# BuSpar®

Tablets, 5 mg and 10 mg

(buspirone HCl)

*for a different kind of calm*

*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

**For Brief Summary, please see following page.**

© 1989, Bristol-Myers Company, Evansville, Indiana 47721, U.S.A.

MJL8-4270

# BuSpar® (buspirone HCl)

**References:** 1. Newton RE, *et al.* A review of the side effect profile of buspirone. *Am J Med* 1986;80(3B):17-21. 2. Luckii I, *et al.* Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. 3. Lader M: Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(5A):20-26

**Contraindications:** Hypersensitivity to buspirone hydrochloride.

**Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard.** Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

**Precautions:** ***General***—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

*Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients:* Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

*Possible concerns related to buspirone's binding to dopamine receptors:* Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

***Information for Patients***—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

***Drug Interactions***—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

***Carcinogenesis, Mutagenesis, Impairment of Fertility***—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

***Pregnancy: Teratogenic Effects***—Pregnancy Category B: Should be used during pregnancy only if clearly needed.

***Nursing Mothers***—Administration to nursing women should be avoided if clinically possible.

***Pediatric Use***—The safety and effectiveness have not been determined in individuals below 18 years of age.

***Use in the Elderly***—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

***Use in Patients with Impaired Hepatic or Renal Function***—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

**Adverse Reactions (See also Precautions):** ***Commonly Observed***—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

***Associated with Discontinuation of Treatment***—The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

***Incidence in Controlled Clinical Trials***—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

***Other Events Observed During the Entire Premarketing Evaluation***—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

***Postintroduction Clinical Experience***—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

**Drug Abuse and Dependence:** ***Controlled Substance Class***—Not a controlled substance.

***Physical and Psychological Dependence***—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

**Overdosage:** ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

***Recommended Overdose Treatment***—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

*For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.*

U.S. Patent Nos. 3,717,634 and 4,182,763

MJL8-4270

Mead Johnson PHARMACEUTICALS

A Bristol-Myers Company
Evansville, Indiana 47721



# USING IT WON'T KILL YOU. NOT USING IT MIGHT.

Maybe you don't like using condoms. But if you're going to have sex, a latex condom with a spermicide is your best protection against the AIDS virus.

Use them every time, from start to finish, according to the manufacturers' directions. Because no one has ever been cured of AIDS. More than 40,000 Americans have already died from it.

And even if you don't like condoms, using them is definitely better than that.

**HELP STOP AIDS. USE A CONDOM.**

AMERICAN FOUNDATION FOR AIDS RESEARCH

Ad Council — A Public Service of This Publication & The Advertising Council

NATIONAL AIDS NETWORK

Photo: Jerry Friedman

©1988, The Ad Council.

# PUT YOUR MEDICAL CAREER IN FLIGHT.

Discover the thrill of flying, the end of office overhead and the enjoyment of a general practice as an Air Force flight surgeon. Talk to an Air Force medical program manager about the tremendous benefits of being an Air Force medical officer:

- Quality lifestyle, quality practice
- 30 days vacation with pay per year
- Support of skilled professionals
- Non-contributing retirement plan if qualified

Discover how to take flight as an Air Force flight surgeon. Talk to the Air Force medical team today. Call

**USAF**
**HEALTH PROFESSIONS**
**TOLL FREE**
**1-800-423-USAF**

AIR FORCE

(Continued from Page 654)

704 **Single-Photon-Emission Computed Tomography Using Cerebral Perfusion**
WILLIAM L. ASHBURN, MD

705 **Single-Photon-Emission Computed Tomography of Myocardial Perfusion and the Hepatic Blood Pool**
DAVID H. LEWIS, MD, and WIL B. NELP, MD

706 **Gastric Emptying Revisited**
GERALD KIRK, MD

707 **Hepatobiliary Excretion Scintigraphy Revisited**
WALTER H. WILLIAMS, PhD, MD

707 **Captopril Renograms for Detecting Renovascular Hypertension**
JOHN MAX VOGEL, MD

708 **Dacryoscintigraphy Revisited**
KENNETH P. LYONS, MD; BRUCE BECKER, MD; and KENNETH ASHTON, MD

708 **Radiolabeled Monoclonal Antibodies for Detecting and Treating Cancer**
DAVID C. P. CHEN, MD, and MICHAEL E. SIEGEL, MD

709 **Treatment of Bone Metastases**
ROBERT F. CARRETTA, MD

709 **Radionuclide Synovectomy for Chronic Joint Effusion**
MICHAEL E. SIEGEL, MD

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON, MA
JUN 2 6 1990

## EDITORIALS

711 **Medicine in Extraordinary Times**

711 **Kidney Transplant Revisited (1990)**
WILLIAM J. C. AMEND, Jr, MD
*Dr Amend is Clinical Professor of Medicine, University of California, San Francisco, School of Medicine.*

## CASE REPORTS

714 **Acute Pancreatitis Associated With High-Dose Interleukin-2 Immunotherapy for Malignant Melanoma**
GEORGE R. BIRCHFIELD, MD; JOHN H. WARD, MD; BRUCE G. REDMAN, DO; LAWRENCE FLAHERTY, MD; and WOLFRAM E. SAMLOWSKI, MD
*From the Division of Hematology/Oncology, University of Utah School of Medicine, Salt Lake City; the Division of Hematology/Oncology, Wayne State University School of Medicine, Detroit; and the Veterans Administration Medical Center, Salt Lake City.*

716 **Rhabdomyolysis and *Staphylococcus aureus* Septicemia in a Man With the Acquired Immunodeficiency Syndrome**
ALBERT W. WU, MD; KURT BENIRSCHKE, MD; and J. ALLEN McCUTCHAN, MD
*From the Robert Wood Johnson/Veterans Administration Clinical Scholars Program, University of California, San Francisco, and the Departments of Pathology and Medicine, University of California, San Diego, School of Medicine, La Jolla.*

719 **Capgras's Syndrome Associated With Sensory Loss**
STEPHEN F. SIGNER, MD; PAUL C. VAN NESS, MD; and R. JEFFREY DAVIS, DO
*From the Department of Psychiatry, University of Ottawa School of Medicine and Royal Ottawa Hospital, Ontario, Canada; the Department of Neurology, The Cleveland Clinic Foundation, Cleveland; and the Neurobehavior Unit, Canyon Springs Hospital, Rancho Mirage, California.*

(Continued on Page 662)

ONCE-A-DAY

# Calan® SR

(verapamil HCl)

SUSTAINED-RELEASE **CAPLETS**

180mg

240mg

## BEYOND YOUR EXPECTATIONS:

## SINGLE-AGENT SUCCESS!*[1-6]

**New recommended starting dose**
for newly diagnosed hypertensives†...
**NEW 180-mg CAPLET once daily**

**SEARLE**

*In mild to moderate hypertension.

†Lower initial doses of 120 mg a day may be warranted in patients who may have an increased response to verapamil (eg, the elderly or small people). Please see next page of this advertisement for references and a brief summary of prescribing information.

© 1990, G.D. Searle & Co. A90-W142T

# 80% SINGLE-AGENT SUCCESS

## ☐ SIX CLINICAL TRIALS ☐ MORE THAN 4,000 PATIENTS ☐ REGARDLESS OF AGE* OR RACE

| Success Rate | Author | Patient Population | Age Range | Goal DBP | Duration of Therapy |
|---|---|---|---|---|---|
| 82% | Reinfrank et al[1] | 97 patients; mild, moderate, severe, and isolated systolic HT | 18-70 | <95 mm Hg | 12 weeks |
| 83% | Saunders et al[2] | 54 black patients; mild to moderate HT | 18-70 | <90 mm Hg or ≥10 mm Hg reduction | 8 weeks |
| 84% | Speders et al[3] | 3,741 patients; mild, moderate, and severe HT | 30-70 | ≤90 mm Hg | 6 weeks |
| 84% | Henry et al[4] | 51 patients; mild to moderate HT | 21-75 | ≤90 mm Hg or ≥15 mm Hg reduction | 4 months |
| 86% | Midtbo et al[5] | 22 patients; mild to moderate HT | 33-64 | <90 mm Hg | 4 weeks |
| 88% | Bochsler et al[6] | 43 patients; mild to moderate HT | 21-70 | ≤90 mm Hg or ≥15 mm Hg reduction | 4 months |

HT = hypertension
*For adult hypertensives only.

Constipation, which can be easily managed in most patients, is the most frequently reported side effect of Calan SR.

ONCE-A-DAY
**Calan® SR**
(verapamil HCl) 180mg 240mg
SUSTAINED RELEASE CAPLETS

## THE 80% SOLUTION

**BRIEF SUMMARY**

**Contraindications:** Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

**Warnings:** Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%) Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

**Precautions:** Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring Decreased metoprolol clearance may occur with combined use Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability Phenobarbital may increase verapamil clearance Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing), dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

**Adverse Reactions:** Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence.

12/21/89 • P90 W198V

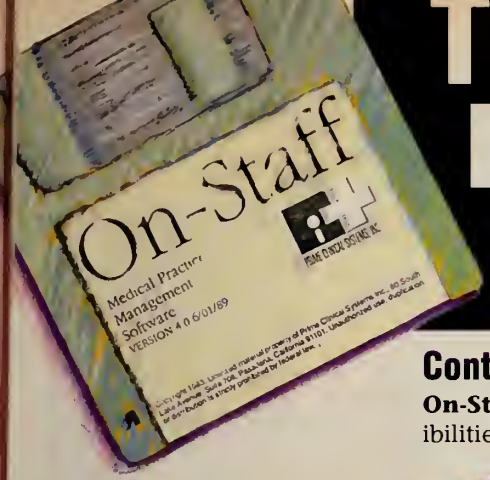

**References:**
1. Reinfrank J, Eckardt A, Schneider G, et al: Long term efficacy and safety of verapamil SR 240 mg in hypertension. *Acta Therapeutica* 1989;15:221-235. 2. Saunders E, Weir MR, Kong BW, et al: A comparison of the efficacy and safety of a beta blocker, calcium channel blocker, and converting enzyme inhibitor in hypertensive blacks. *Arch Intern Med* (accepted for publication). 3. Speders S, Sosna J, Schumacher A, et al: Efficacy and safety of verapamil SR 240 mg in essential hypertension: Results of a multicentric phase IV study. *J Cardiovasc Pharmacol* 1989;13 (suppl 4):S47-S49. 4. Henry JA, Chester PC, Latham AN: Sustained-release verapamil or atenolol in essential hypertension. *J Drug Dev* 1988;1:69-75. 5. Midtbo KA, Hals O, Louve O: A new sustained-release formulation of verapamil in the treatment of hypertension. *J Clin Hypertens* 1986;3:125S-132S. 6. Bochsler JA, Simmons RL, Ward PJ, et al: Verapamil SR and propranolol LA: A comparison of efficacy and side effects in the treatment of mild to moderate hypertension. *J Hum Hypertens* 1988;1:305-310


A90 W1421

**SEARLE**

G.D Searle & Co
Box 5110, Chicago, IL 60680

*Address medical inquiries to*
*G.D Searle & Co*
*Medical & Scientific*
*Information Department*
*4901 Searle Parkway*
*Skokie, IL 60077*



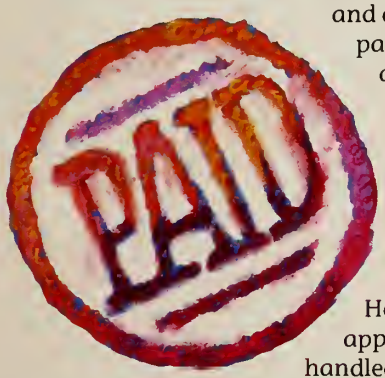

# Take Control Every Day in Every Way

## On-Staff™... for Powerful, Sensible Practice Management

Examine **On-Staff**, the industry's most powerful and easy to use medical practice management system. Whether you're a solo practitioner or manage multi-specialty clinics, **On-Staff** software gives you more ways to control every aspect of your medical practice from patient scheduling to the final payment posting.

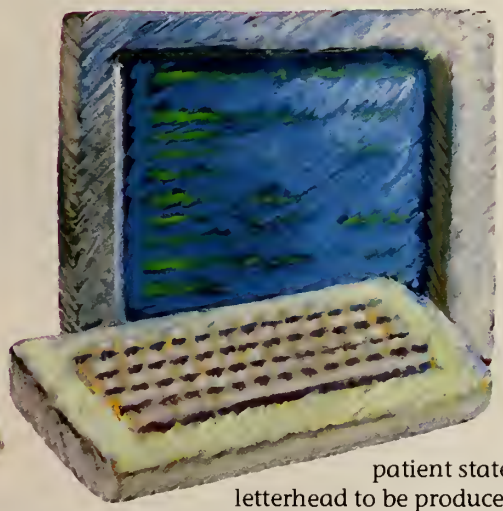
## Control Receivables

**On-Staff** computes the financial responsibilities of insurance carriers versus patients, and effectively monitors payments and adjustments. The system is specifically designed to speed the collection process. **On-Staff** automates not just billing, but also the whole range of follow-up routines. Hence, insurance tracers, appeal letters, etc. are all handled automatically.




## Control Information

**On-Staff** comes preprogrammed to supply you with all the standard reports, but it can also provide you with virtually any other kind of information on demand: you may want a list of patients with a particular ailment within specific zip codes, or wish to identify insurance companies with a bad record of payments. Just define your criteria in plain English, and watch **On-Staff** deliver, instantaneously.



## Control Your Office

**On-Staff** interacts with a variety of wordprocessing and spreadsheet programs to simplify your office work and help you get the most out of your computing investment. **On-Staff's** "forms generator" allows insurance claim forms, patient statements, and even your letterhead to be produced from plain paper.

## Control Communications

**On-Staff** offers a sensitive system for business communication. So, whether it is requesting a patient to meet his deductible, or responding to a denial by an insurance carrier, **On-Staff** generates a precise and personal letter for the right party automatically.

☐ Yes, I would like to take control of my daily administration with a **FREE** demonstration.
☐ Yes, I would like a copy of your **FREE On-Staff** brochure.
☐ No, I would not like to take control. My office is running at peak efficiency.

Best time to call _____ AM/PM
Phone ( ) _____
Name _____
Title _____
Address _____
City _____ State _____ Zip _____

☐ I currently have a computer system in place.
☐ I do not have a computer system in place.

PRIME CLINICAL SYSTEMS, INC.

Prime Clinical
80 South Lake Avenue
Pasadena, CA 91101
**1-800-523-5977**

WJM

## Control Your Future

Send in the information card or call toll free **1-800-523-5977** today for a free brochure or an **On-Staff** demonstration to address your specific needs.

IBM Business Partner

**On-Staff** is a trademark of Prime Clinical Systems.
IBM is a registered trademark of International Business Machines.

(Continued from Page 658)

## CORRESPONDENCE

721 **Patient's Presence in Prenatal Screening**
BERTHOLD E. UMLAND, MD

721 ***Blastocystis hominis***
EDWARD K. MARKELL, PhD, MD, and MICHAEL P. UDKOW, MD

721 **Espresso Maker's Wrist**
DENNIS SHUSTERMAN, MD, MPH

722 **A Pathologist's View of Mohs' Micrographic Surgery**
RICHARD E. SAFRIN, MD

722 **Ruminations of an Aspiring Californian**
ALBERT W. WU, MD, and HAYA R. RUBIN, MD, PhD

723 **Putting Practice Into Law**
JEOFFRY B. GORDON, MD, MPH

723 **Zinc**
H. A. RONAGHY, MD

723 **Confidential and Anonymous Testing**
JAMES P. KRAJESKI, MD

## HEALTH CARE DELIVERY

725 **Low-Birth-Weight Effects of Demographic and Socioeconomic Variables and Prenatal Care in Pima County, Arizona**
IVY L. SCHWARTZ, MD
*From the Department of Family and Community Medicine, Section of Preventive Medicine, University of Arizona College of Medicine, Tucson.*

## MEDICINE IN PERSPECTIVE

729 **Trench Foot—A Study in Military-Medical Responsiveness in the Great War, 1914-1918**
JOHN S. HALLER, Jr
*From the Department of History, University of Colorado, and the Department of Preventive Medicine and Biometrics, University of Colorado Health Sciences Center, Denver.*

## SPECIAL EDITORIALS

734 **A Tribute to MSMW**
DWIGHT L. WILBUR, MD
LLOYD H. SMITH, Jr, MD
LINDA HAWES CLEVER, MD

## OTHER FEATURES

653 **Subscription Information**

664 **Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming**

738 **Volume Index**

747 **Classified Advertising**

756 **Western State Medical Associations' Meetings**

★ **Official Journal of the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.**

★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

*Because safety cannot be taken for granted in $H_2$-antagonist therapy*

# AXID®
## nizatidine

## *Minimal potential for drug interactions*

***Unlike cimetidine and ranitidine,[1] Axid does not inhibit the cytochrome P-450 metabolizing enzyme system.[2]***

## *Swift and effective $H_2$-antagonist therapy*

- *Most patients experience pain relief with the first dose[3]*
- *Heals duodenal ulcer rapidly and effectively[4,5]*
- *Dosage for adults with active duodenal ulcer is 300 mg once nightly (150 mg b.i.d. is also available)*


*References*

1. USP DI Update, September/October 1988, p 120.
2. Br J Clin Pharmacol 1985;20:710-713.
3. Data on file, Lilly Research Laboratories.
4. Scand J Gastroenterol 1987;22(suppl 136):61-70.
5. Am J Gastroenterol 1989;84:769-774.


**AXID®**
nizatidine capsules

**Brief Summary. Consult the package literature for complete information.**

**Indications and Usage:** 1. *Active duodenal ulcer*—for up to eight weeks of treatment. Most patients heal within four weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a reduced dosage of 150 mg h.s. The consequences of therapy with Axid for longer than one year are not known.

**Contraindication:** Known hypersensitivity to the drug. Use with caution in patients with hypersensitivity to other $H_2$-receptor antagonists.

**Precautions:** *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

*Laboratory Tests*—False-positive tests for urobilinogen with Multistix® may occur during therapy.

*Drug Interactions*—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

*Carcinogenesis, Mutagenesis, Impairment of Fertility*—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

*Pregnancy—Teratogenic Effects—Pregnancy Category C*—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Nursing Mothers*—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

*Pediatric Use*—Safety and effectiveness in children have not been established.

*Use in Elderly Patients*—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

**Adverse Reactions:** Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events was due to the drug.

*Hepatic*—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to three times the upper limit of normal, however, did not significantly differ from that in placebo patients. Hepatitis and jaundice have been reported. All abnormalities were reversible after discontinuation of Axid.

*Cardiovascular*—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

*CNS*—Rare cases of reversible mental confusion have been reported.

*Endocrine*—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

*Hematologic*—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another $H_2$-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

*Integumental*—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

*Hypersensitivity*—As with other $H_2$-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Because cross-sensitivity among this class has been observed, $H_2$-receptor antagonists should not be administered to those with a history of hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

*Other*—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

**Overdosage:** Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

PV 2098 AMP [091289]

*Additional information available to the profession on request.*

Lilly

**Eli Lilly and Company**
Indianapolis, Indiana
46285

NZ-2924-B-049310

© 1990, ELI LILLY AND COMPANY

Axid® (nizatidine, Lilly)

Axid® (nizatidine, Lilly)

Axid® (nizatidine, Lilly)

# Continuing Medical Education

**ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING**

## ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

June 15-16—**Understanding Emergency Drugs for the 1990s.** Phoenix Baptist Hospital and Medical Center at Fountain Suites Hotel, Phoenix. Fri-Sat. Contact: Brian Helander, RN, BSc, CEN, (602) 230-7569

June 22-24—**Thirteenth Annual Pediatrics in the Red Rocks.** American Academy of Pediatrics—Arizona Chapter at Los Abrigados, Sedona. Fri-Sun. Contact: Melanye Wrighton, (602) 230-1949.

September 8-9—**Pulmonary and Infectious Diseases.** Mayo Clinic-Scottsdale at Los Abrigados Resort, Sedona. Sat-Sun. Contact: Jodi Lee Smith, (602) 391-8300.

October 19-20—**Common Clinical Problems in the Elderly and Nursing Home Care.** Arizona Geriatrics Society at Arizona Golf Resort and Conference Center, Mesa. Fri-Sat. Contact: Marian Richardson, (602) 974-4212.

### CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

## CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

### ALLERGY

September 15—**Diagnostic and Therapeutic Choices in Allergy and Immunology.** Los Angeles Society of Allergy and Clinical Immunology at Regent Beverly Wilshire Hotel, Beverly Hills. Sat. 8 hrs. Contact: Sherri Cartwright, 1626 N Wilcox, No 557, Hollywood 90028. (818) 240-6735.

### ANESTHESIOLOGY

September 8-9—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Lake Tahoe, California. Sat-Sun. 20 hrs. $175. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

October 28-November 2—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Kaanapali Beach, Hawaii. Sun-Fri. 20 hrs. $345. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

### CARDIOLOGY

June 15-16—**Series IV—Cardiac Wellness and Rehabilitation.** Medical Education Resources at Hyatt Union Square, San Francisco. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

June 22-23—**Series I—Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (303) 798-9682.

August 3-4—**Series II—Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Anaheim. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

August 17-18—**Series IV—Cardiac Wellness and Rehabilitation.** Medical Education Resources at Monterey. Fri-Sat. Contact: MER, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

### KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Avenue, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

*(Continued on Page 666)*

# The Last Thing A Small Business Needs Is A Surprise.

## INTRODUCING NO-SURPRISE™ BUSINESS CHECKING. NO PER-CHECK CHARGES, NO OVERDRAFTS.

Once again, Wells Fargo breaks from the pack by introducing business checking with no per-check charges and automatic overdraft protection. No-Surprise Business Checking is especially designed for small business and Wells Fargo is the only major California bank to offer it.

No-Surprise Business Checking means no per-check charges. There's only one flat monthly checking fee, which can be automatically waived by your account balances.

And no more worries about accidental overdrafts. Now you can have automatic protection from your Wells Fargo Business Savings or Market Rate Account.™

New No-Surprise Business Checking. It's only common sense. And it's only at Wells Fargo. To set up your account, talk to a Business Banker™ at your local Wells Fargo office today.

For more information, call 1-800-642-BANK, ext. 504.

Wells Fargo comes through for small business again.

**WELLS FARGO BANK**

©1990, WFB

Applies to California residents only.

Member FDIC

CONTINUING MEDICAL EDUCATION

(Continued from Page 664)

## DERMATOLOGY

August 3-4—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

August 16-19—**Advanced Seminars in Dermatology.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sun. Contact: UCSD.

## EMERGENCY MEDICINE

June 25-29—**Emergency Medicine Symposium III: Pediatrics.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $450. Contact: UCSD.

August 1-5—**Wilderness Medicine: '90.** American College of Emergency Physicians at Squaw Valley Lake Tahoe, Nevada. Wed-Sun. 22 hrs. $395. Contact: Eugene Allred, MD, PO Box 321, Yreka 96097. (800) 888-5632.

August 20-24—**Emergency Medicine Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 11-13—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Hyatt Union Square. Thurs-Sat. 15 hrs. $375. Contact: UCSF.

October 22-26—**Postgraduate Institute for Primary Care and Emergency Physicians Symposium I: Cardiology, Pulmonary, Neurology.** Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 29-November 3—**Topics in Emergency Medicine.** UCSF at Holiday Inn Golden Gate. Mon-Sat. 32 hrs. $460. Contact: UCSF.

November 12-16—**Emergency Medicine Symposium III: Pediatrics, OB/GYN, Legal Aspects, Dermatology.** UCSD at Hyatt Regency, La Jolla. Mon-Fri. 32 hrs. $450. Contact: UCSD.

## FAMILY PRACTICE/PRIMARY CARE

June 27—**AIDS Update for Primary Care: New Hope in a New Era.** Alta Bates-Herrick Hospital at Hospital Auditorium. Wed. 7 hrs. $115. Contact: Mary Grimm, Medical Education Coordinator, (415) 540-1420.

June 29-July 1—**34th Annual Postgraduate Symposium Family Medicine Update: 1990.** San Diego Academy of Family Physicians at San Diego Marriott. Fri-Sun. 16 hrs. $200. Contact: Barbara Wilcox, PO Box 19641, San Diego 92119. (619) 464-2422.

July 8-11—**Family Practice Board Review.** UCSD at San Diego Hilton Beach & Tennis Resort, San Diego. Sun-Wed. 22 hrs. $350. Contact: UCSD.

July 9-12—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Thurs. 25 hrs. Contact: UCSF.

July 19-21—**Rheumatology and Arthritis: A Conference for Primary Care Physicians.** Sharp Memorial Hospital at Catamaran Resort Hotel, San Diego. Thurs-Sat. 13 hrs. $250. Contact: Sharp Memorial Hospital, 7901 Frost St, San Diego 92123. (619) 541-3525.

August 24-26—**3rd Coronado Summer Conference on Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien Hotel Coronado Island, San Diego. Fri-Sun. 15 hrs. $275. Contact: Heidi Jurgens, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 3-5—**Primary Care Medicine: Principles and Practice.** UCSF at Holiday Inn Golden Gateway, San Francisco. Wed-Fri. 19 hrs. $425. Contact: UCSF.

## INTERNAL MEDICINE

June 25-30—**Advances in Internal Medicine.** UCSF at Cole Hall, San Francisco. Tues-Sat. 32 hrs. $535. Contact: UCSF.

August 19-24—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. Contact: UCD.

September 14-16—**Gastroenterology.** UCSF at San Francisco Hilton and Towers. Fri-Sun. 17 hrs. $415. Contact: UCSF.

October 18-20—**Breast Cancer Seminar.** Memorial/UCI Center for Health Education at Stouffer Hotel, Palm Springs. Thurs-Sat. Contact: UCI.

November 9-10—**Metabolic Control of Diabetes.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. Fri-Sat. Contact: UCI.

## OB/GYN

August 17-19—**3rd Annual Perinatal Review.** Memorial/UCI Center for Health Education at Four Seasons Hotel, Newport Beach. Fri-Sun. Contact: UCI.

August 21-25—**8th Annual Controversies in OB/GYN.** Memorial/UCI Center for Health Education at Mauna Kea, Hawaii. Tues-Sat. Contact: UCI.

November 8-11—**Current Issues in Perinatal Medicine.** Memorial/UCI Center for Health Education at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sun. Contact: UCI.

November 11-17—**13th Annual Review Course in Clinical OB/GYN and/or Gynecological Histopathology.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. 1 week. Contact: UCI.

November 29-December 1—**Nebraska OB/GYN Society Meeting.** Nebraska OB/GYN at Las Vegas, Nevada. Thurs-Sat. Contact: University of Nebraska Medical Center, 42nd and Dewey Ave, Omaha, NE 68105-1065. (402) 559-4152.

## OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

July 23-27—**4th Annual Sports Medicine.** UCSD at San Diego Princess. Mon-Fri. 22 hrs. $350. Contact: UCSD.

October 2-7—**Sports Medicine Update.** Memorial/UCI Center for Health Education at Mauna Kea Hotel, Hawaii. Tues-Sun. Contact: UCI.

October 8-19—**Occupational and Environmental Medicine Session II.** UCSF at Cathedral Hill Hotel, San Francisco. 1½ weeks. 80 hours. $1,200. Contact: UCSF.

October 15-19—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

## OPHTHALMOLOGY

August 26-30—**Ophthalmology Update: 1990.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

August 26-29—**External Disease: Diagnosis and Management for the 1990's.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Wed. 13 hrs. $350. Contact: UCD.

September 14-16—**Uveitis/Retinal Frontiers: Diagnostic, Medical and Surgical Approaches to Uveitis.** UCSF at Carmel Valley Ranch Resort. Wed-Fri. Contact: UCSF.

November 30-December 2—**American Academy of Ophthalmology Regional Update Course.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, (213) 825-9508.

## ORTHOPAEDICS

October 4-6—**Orthopaedic Update.** UCSD at Hyatt La Jolla. Thurs-Sat. Contact: Pat Curl, PO Box 33185, San Diego 92103. (619) 692-9115.

## PATHOLOGY

October 4-6—**International Symposium on Medical Virology.** UCI at Four Seasons Hotel, Newport Beach. Thurs-Sat. Contact: Luis M. de la Maza, (714) 634-6868.

October 12-14—**8th Postgraduate Course in Medical Mycology (Dermatomycology).** UCSF. Fri-Sun. 16 hrs. Contact: UCSF.

October 19—**Fine Needle Aspiration Tutorials.** UCSF. Fri. 7 hrs. Contact: UCSF.

(Continued on Page 668)

# What we've done for you lately.

We've taken some concrete steps toward making the less exciting parts of your job less of a problem.

Here's what we did.

We developed ways to speed up claims processing and payments. So you can spend more time worrying about patients, and less time worrying about paperwork.

Our new One Call system helps speed up utilization review and preauthorization. So you can get immediate answers to your benefit and eligibility questions with just one call.

And without being transferred or put on hold.

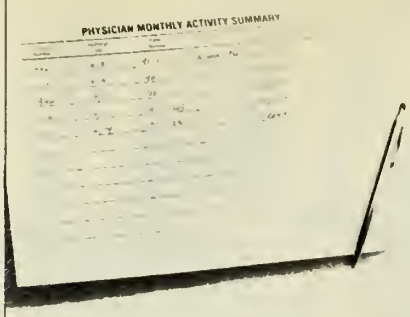
We've also developed a program called Claim Free™, which further expedites the reimbursement process by eliminating paper claims for both you and your Medicare subscribers.

We're continuing to make these changes for one simple reason: The whole point of health care is to take care of people.

And, by taking better care of you, we're doing just that.

**Blue Cross of California**

We care about what's good for you.




Oct 30 - Nov 3, 1990
Capitol Plaza Holiday Inn
Sacramento, CA

**IF QUALITY OF CARE IS IMPORTANT TO YOU, CONSIDER A CAREER IN ADMINISTRATIVE MEDICINE.**

A medical directorship directly involves you in quality issues important to physicians and patients. Learn to adapt your personal leadership style to a new role in administrative medicine. Our four-day interactional career enhancement program for physicians can help you move comfortably within an organization. You'll practice techniques that help you control meetings, respond successfully to confrontation, and come out ahead in negotiations. And you'll learn how to meet QA and Joint Commission requirements. Career counseling is available upon completion of the program. Class is limited to 24 participants. Call today for more information.

**M**edical **D**irectors
**A**dvancement **C**ouncil
An Education and Executive Search Service
Two Shannon Court
Chico, California 95928

**Call our toll-free number for more information. 1-800-762-2595.**

C.M.E. credits applied for.


CONTINUING MEDICAL EDUCATION

*(Continued from Page 666)*

October 20—**30th Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Wyndham Palm Springs. Sat. Contact: Sylvie Tarro, 5777 W Century Blvd, Ste 395, Los Angeles 90045. (213) 641-8152.

November 2-3—**Update on Thyroid Disease—1990.** UCSF at Hyatt Regency Embarcadero, San Francisco. Fri-Sat. 12 hrs. $150. Contact: UCSF.

## PEDIATRICS

June 29-30—**Current Concepts in Pediatric Allergy and Otolaryngology.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sat. Contact: Continuing Medical Education Office, Children's Hospital, (619) 576-4072.

September 7-8—**Pediatrics and Environmental Health: The Pediatrician as Investigator, Educator, and Advocate.** Children's Hospital Oakland at Berkeley Conference Center. Fri-Sat. 12 hrs. $85. Contact: Joy Carlson, EPI Training Project, 5900 Hollis St, No. E, Emeryville 94608. (415) 540-3657.

October 7-14—**15th Annual Pediatrics for the Practitioner.** Memorial/UCI Center for Health Education at Mauna Kea Hotel, Hawaii. 1 week. Contact: UCI.

November 9-11—**Infectious Diseases in Children.** Children's Hospital Oakland at Monterey Plaza Hotel on Cannery Row. Fri-Sun. 12 hrs. $280. Contact: Kim Leadon, 747 52nd St, Oakland 94609. (415) 428-3021.

## PSYCHIATRY

August 2-4—**Sexual Problems of Adults Molested as Children.** UCLA at Disneyland Hotel, Anaheim. Thurs-Sat. 13 hrs. $375. Contact: UCLA.

October 19-21—**Creating an Integrated Psychiatry: Challenge of the 90's.** California Psychiatric Association at Claremont Hotel, Berkeley. Fri-Sun. 11 hrs. Contact: Barbara Gard, 1100 N St, Ste 2-E, Sacramento 95814. (916) 442-5196.

November 12-16—**Introduction to Medical Hypnosis.** UCSD at Inn at Del Mar. Mon-Fri. Contact: UCSD.

## RADIOLOGY

July 22-26—**Napa Valley Imaging Update: MRI 1990.** UCD at Silverado Country Club, Napa. Sun-Thurs. 17 hrs. $445. Contact: UCD.

July 23-25—**Musculoskeletal Imaging.** Hoag Memorial Hospital, Department of Radiology at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Wed. 15 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 26-29—**4th Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital, Department of Radiology at Ritz-Carlton Resort Hotel, Laguna Niguel. Thurs-Sun. 22 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 18-19—**Intravascular Ultrasound Imaging.** Memorial/UCI Center for Health Education at Anaheim Hilton Hotel. Sat-Sun. Contact: UCI.

August 23-28—**6th Annual Physics and Biology of Radiology.** UCSD at Hanalei Hotel, San Diego. Thurs-Tues. 25 hrs. $395. Contact: UCSD.

September 7-10—**6th Annual Sonography Update for Physicians and Sonographers.** UCSD at Hotel del Coronado, San Diego. Fri-Mon. 18 hrs. $375. Contact: UCSD.

October 6-7—**Ultrasound: 1990.** UCD at Red Lion Inn, Sacramento. Sat-Sun. Contact: UCD.

October 20-21—**Advanced Imaging of the Musculoskeletal System.** UCSD at Hotel del Coronado. Sat-Sun. 12 hrs. $125. Contact: UCSD.

October 22-26—**15th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $300. Contact: UCSD.

October 26-28—**10th Annual Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 18 hrs. $350. Contact: UCSD.

*(Continued on Page 670)*

# PRO TECTION

## MALPRACTICE COVERAGE AT ITS BEST

- Effective and experienced management.
- An improved cash flow position immediately.
- $1 million per occurrence/$3 million aggregate per year.
- Affordable retroactive coverage.
- Remedial medical services designed to alleviate adverse medical/surgical results.

## COMPARE AND SAVE

For further information, please call or write:

PHYSICIANS
INTERINDEMNITY

310 E. Colorado Street, Suite 308, Glendale, California 91205-1633
(818) 241-5119

**Advances In Medicine**
July 24-27, 1990
**The Snowmass Conference Center**
**Snowmass, Colorado**

**Program Sponsors:** The University of Nebraska College of Medicine Alumni Association in cooperation with the Center for Continuing Education.

**Topics Will Include:** Surgery, ENT, Radiology, Endocrinology, Transplantation, Cardiovascular Disease Prevention, Management of Obesity, Infertility, and AIDS.

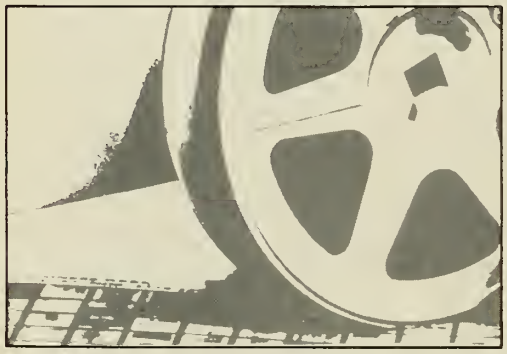
Health care and medical education in the Twenty-first Century - Teaching physicians to critically assess the value of futuristic medical concepts.

**Credit:** 11 1/2 hours, AMA Category I and AAFP Prescribed. (Mornings only - afternoons free)

**Location:** Snowmass, Colorado, nestled high in the Colorado Rockies, just 14 miles from Aspen. Excellent flight service into Aspen Airport. There are many cultural and outdoor activities for all age groups.

**For Further Information,** please contact Marge Adey, Center for Continuing Education at (402) 559-4152 or Amy Peters, Alumni Office at (402) 556-4745, University of Nebraska Medical Center, 600 South 42nd Street, Omaha, Nebraska 68198-6100.

**This Publication is available in Microform.**



**University Microfilms International**

Please send additional information
for _____ (name of publication)
Name _____
Institution _____
Street _____
City _____
State _____ Zip _____
300 North Zeeb Road, Dept P.R., Ann Arbor, Mi 48106

## CONTINUING MEDICAL EDUCATION

*(Continued from Page 668)*

November 9-11—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 20 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

### SURGERY

June 1990-December 1990—**Temporal Bone Surgical Dissection Courses: 1990.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

June 1990—**Microsurgery Training Courses.** UCSD at Grossmont Hospital, La Mesa. 40 hrs. $1,125. Contact: UCSD.

June 17-22—**Anatomic Basis for Aesthetic Surgery: Hands-On Laboratory Course.** UCD at Hyatt Regency, Sacramento. Sun-Fri. Contact: UCD.

June 21-23—**7th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Medical Center at La Jolla Marriott Hotel. Thurs-Sat. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 598-0080.

June 28-30—**Contemporary Concepts in Total Joint Replacement.** Memorial/UCI Center for Health Education at Dana Point Resort. Thurs-Sat. Contact: UCI.

July 17-21—**6th Annual Superficial Anatomy and Cutaneous Surgery.** UCSD at La Jolla Marriott. Tues-Sat. Contact: UCSD.

August 8-11—**Sharp Surgical Review Course.** Sharp Memorial Hospital at Le Meridien Hotel, San Diego. Wed-Sat. 14 hrs. $350. Contact: Sharp Memorial, 7901 Frost St, San Diego 92123. (619) 541-3525.

October 6-8—**Anatomic Basis for Aesthetic Surgery: Hands-On Laboratory Course.** UCD at Hyatt Regency, Davis. Sat-Mon. Contact: UCD.

### OF INTEREST TO ALL PHYSICIANS

June 21-23—**Nevada State Medical Association Annual Meeting.** Nevada State Medical Association at Hyatt Lake Tahoe, Nevada. Thurs-Sat. Contact: Nevada State Medical Association, 3660 Baker Lane, Reno, NV 89509. (702) 825-6788.

July 9-13—**2nd Annual Marine Medicine.** UCSD at San Diego Princess. Mon-Fri. 23 hrs. $375. Contact: UCSD.

July 19-22—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 26 hrs. $295. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077. (404) 641-9773.

July 23-27—**4th Annual Sports Medicine.** UCSD at San Diego Princess. Mon-Fri. Contact: UCSD.

September 10-14—**Hyperbaric Medicine.** UCI/Memorial Medical Center at Long Beach. Mon-Fri. 30 hrs. $650. Contact: Celia Loney, 2801 Atlantic Ave, PO Box 1428, Long Beach 90891. (213) 595-2000.

November 12-16—**Hyperbaric Medicine.** UCI/Memorial Medical Center at Long Beach. Mon-Fri. 30 hrs. $650. Contact: Celia Loney, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801. (213) 595-2000.

## COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

June 26-28—**Community Health Traineeship.** The Children's Hospital, Denver. Tues—Wed. Contact: Christie Sievers, (303) 861-6413.

June 30-July 3—**Renal Disease for the Internist and Nephrologist.** U of Colo at the Given Institute, Aspen. Sat-Tues. Contact: U of Colo.

*(Continued on Page 672)*

# Our commitment to America's physicians: WE'RE IN IT TOGETHER.

Protect your practice with the financial strength only a national leader can provide. The Doctors' Company is the largest independent physician-owned and physician-governed professional liability insurer in America. We understand the issues you face and the concerns of practice management.

- Competitive premiums
- Risk management programs
- Tailored Group Practice programs with savings of 20% or more

An A+ (Q) (Superior) rating has been awarded The Doctors' Company by A.M. Best Company, independent analysts for the insurance industry. No higher rating is possible. We are endorsed by medical societies and associations throughout the nation.

Our primary reason for being is to meet your needs in these challenging times. As physicians ourselves, we would not envision doing anything less.

THE DOCTORS' COMPANY

More than 14,000 physicians call The Doctors' Company *their* company.

For referral to your local representative call:
(California) 800-352-7271 (Other States) 800-421-2368

Note: Not all specialties are insured in every state.

## CONTINUING MEDICAL EDUCATION

*(Continued from Page 670)*

July 6-7—**Western Slope Conference.** The Children's Hospital at Manor Vail, Vail. Fri-Sat. Contact: Christie Sievers, (303) 681-6413.

July 8-13—**25th Annual Internal Medicine Program.** U of Colo at YMCA of the Rockies, Estes Park. Mon-Fri. Contact: U of Colo.

July 11-12—**Physician Preceptorship Program.** The Children's Hospital, Denver. Wed-Thurs. Contact: Pat Winter, (303) 861-6668.

July 18-21—**Insulin Dependent Diabetes.** Barbara Davis Center for Childhood Diabetes, the Children's Diabetes Foundation, and CU School of Medicine at Keystone Inn, Keystone. Wed-Sat. Contact: U of Colo.

July 23-27—**3rd Annual Colorado Geriatric Symposium.** U of Colo at the Given Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 30-August 3—**Dynamic Psychotherapy.** U of Colo at the Given Institute, Aspen. Mon-Fri. Contact: U of Colo.

August 5-9—**Annual Pediatric Program.** U of Colo at the Given Institute, Aspen. Sun-Thurs. Contact: U of Colo.

August 6-8—**Newborn Respiratory Therapy Traineeship.** The Children's Hospital, Denver. Mon-Wed. Contact: Jeff Griebel, (303) 861-6227.

August 6-10—**Respiratory Therapy Traineeship.** The Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6227.

August 12-18—**Annual Primary Care Orthopedics.** U of Colo at the Given Institute, Aspen. One week. Contact: U of Colo.

August 14-18—**Aspen Basic/Clinical Science: Neuroscience.** U of Colo at the Given Institute, Aspen. Tues-Sat. Contact: U of Colo.

August 20-24—**Annual Internal Medicine Board Review.** U of Colo, Denver. Mon-Fri. Contact: U of Colo.

September 4, 11, 18—**OB Nursing in the 1990s.** The Children's Hospital at University Hospital, Denver. Tues. Contact: Trish Beachy, (303) 270-8376.

September 10-14—**Family Practice Review.** U of Colo, Denver. Mon-Fri. Contact: U of Colo.

October 10-11—**Physician Preceptorship Program.** The Children's Hospital, Denver. Wed-Thurs. Contact: Pat Winter, (303) 861-6668.

October 17-19—**Care of the Sick Newborn Conference.** The Children's Hospital, Denver. Wed-Fri. Contact: Conference Dept, Children's Hospital, (303) 861-6945.

October 22-26—**Rural Perinatal Traineeship (Level I).** The Children's Hospital, Denver. Mon-Fri. Contact: Christie Sievers, (303) 861-5413.

November 2-3—**Fort Collins Perinatal Conference.** The Children's Hospital at the Marriott Hotel, Fort Collins. Fri-Sat. Contact: Christie Sievers, (303) 861-6413.

November 9-10—**Western Slope Conference.** The Children's Hospital at the Red Lion Inn, Durango. Fri-Sat. Contact: Christie Sievers, (303) 861-6413.

November 12-16—**Rural Perinatal Traineeship (Level II).** The Children's Hospital, Denver. Mon-Fri. Contact: Christie Sievers, (303) 861-6413.

December 3-7—**Respiratory Therapy Traineeship.** The Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6227.

January—**Perinatal Continuing Education Program.** The Children's Hospital, Denver Community Hospital-based, 40-week, self-study program for all perinatal healthcare providers. Contact: Pat Winter, (303) 861-6668.

### CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

## IDAHO

July 26-28—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sun. Contact: Idaho Medical Association, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

*(Continued on Page 674)*


Specify Adjunctive

**LIBRAX®**

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

* Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
*Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

P.I. 0288

ROCHE® **Roche Products**

Roche Products Inc.
Manati, Puerto Rico 00701

Be sure to specify Librax, "Do not Substitute" or your state's equivalent statement on your prescription.

In IBS,* when it's brain versus bowel,

# IT'S TIME FOR THE PEACEMAKER.

In irritable bowel syndrome,* intestinal discomfort will often erupt in tandem with anxiety—launching a cycle of brain/bowel conflict. Make peace with Librax. Because of possible CNS effects, caution patients about activities requiring complete mental alertness.

*Librax has been evaluated as possibly effective as adjunctive therapy in the treatment of peptic ulcer and IBS.

Specify Adjunctive

**LIBRAX®**

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

ROCHE

Copyright © 1989 by Roche Products Inc. All rights reserved.

Please see summary of prescribing information on adjacent page.

(Continued from Page 672)

## NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

June 14-15—**Psychotherapeutic Interventions With Ethnic Minority Children and Families.** UNM Conference Center, Albuquerque. Thurs-Fri. Contact: UNM SOM, Office of Continuing Medical Education, PO Box 713, Albuquerque 87131. (505) 277-3942.

June 21—**Neonatal Resuscitation.** St Vincent Hospital, Santa Fe. Thurs. Contact: Jennifer Johnson, MD, 455 St Michael's Dr, Santa Fe 87501. (505) 983-3361.

June 22-23—**Third Annual Rocky Mountain Conference on Neuropsychiatry and the Treatment of Persons With Developmental Disabilities.** Marriott Mark Resort, Vail, Colorado. Fri-Sat. Contact: Paul Spragg, MD, JFK Center for Developmental Disabilities, Box C-234, Denver, CO 80262. (303) 270-8826.

July 12-14—**Issues in Primary Pediatric Practice.** Inn At Loretto, Santa Fe. Thurs-Sat. Contact: UNM SOM, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

July 19—**Neonatal Resuscitation.** St Vincent Hospital, Santa Fe. Thurs. Contact: Jennifer Johnson, MD, 455 St Michael's Dr, Santa Fe 87501. (505) 983-3361.

July 19-21—**Current Concepts in General Surgery.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

August 16—**Neonatal Resuscitation.** St Vincent Hospital, Santa Fe. Thurs. Contact: Jennifer Johnson, MD, 455 St Michael's Dr, Santa Fe 87501. (505) 983-3361.

September 6-8—**Perinatal Care Update.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

October 12-13—**John N. Wilson, MD: Lectureship in Cardiovacular Diseases.** Hyatt Regency, Albuquerque. Fri-Sat. Contact: Ann Nelson, Presbyterian Heart Institute Foundation, PO Box 26666, Albuquerque 87125. (505) 841-1225.

## UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

### MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

June 17-22—**School on Alcoholism and Other Drug Dependencies** (Sponsor: UUMC). Sun-Fri. University of Utah, Salt Lake City. Contact: (801) 538-3956.

July 8-14—**Update in Internal Medicine: Board Review Course** (Sponsor: UUMC). Sun-Sat. Cliff Lodge, Snowbird. Contact: (801) 581-8664.

July 25-27—**12th Annual Common Problems in Pediatrics** (Sponsor: UUMC). Wed-Fri. University Park Hotel, Salt Lake City. Contact: (801) 466-3500.

October 4-5—**Ethics and Health** (Sponsor: UUMC). Thurs-Sat. University of Utah Alumni House, Salt Lake City. Contact: (801) 581-8664.

### SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

CONTINUING MEDICAL EDUCATION

(Continued from Page 674)

## WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

June 16—**AIDS Issues 1990.** Kirkland. Sat. Contact: Evergreen Hospital, (206) 823-7599.

June 25-26—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: CME Pierce County.

June 29—**Family Practice Update.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

August 2-4—**Imaging.** Coeur d'Alene Resort. Thurs-Sat. Contact: Sacred Heart Medical Center, Dept of Radiology, (509) 455-3352.

September 20—**Orthopedics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

September 20-21—**Critical Care 90.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

October 11—**Diabetes.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

October 16-19—**Indoor Radon and Lung Cancer: Reality or Myth.** Richland. Tues-Fri. Life Sciences Center, Battelle, Pac NW Lab. (509) 376-3665.

October 19—**24th Annual Cancer Conference: Gastrointestinal Cancer in the 90s.** Seattle. Fri. Contact: VMMC.

October 20—**Practice Update for Rural Physicians.** Seattle. Sat. Contact: VMMC.

November 2—**Diabetes, 1990.** Seattle. Fri. Contact: VMMC.

November 8—**Pediatrics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

November 9—**Medical and Surgical Update for Psychiatrists.** Seattle. Fri. Contact: VMMC.

December 7—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

### COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

## WYOMING

June 14-16—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

August 8-11—**American College of Surgeons, Montana—Wyoming Chapter.** Jackson Hole. Wed-Sat. Contact: Robert C. Ratcliff, MD, 940 E Third St, Casper 82601. (307) 577-4223. ◆


# YOCON®
## YOHIMBINE HCl

**Description:** Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

**Action:** Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

**Indications:** Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

**Contraindications:** Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

**Warning:** Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

**Adverse Reactions:** Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

**Dosage and Administration:** Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

**How Supplied:** Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

**References:**

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85

AVAILABLE AT PHARMACIES NATIONWIDE

**PALISADES PHARMACEUTICALS, INC.**
219 County Road
Tenafly, New Jersey 07670
**(201) 569-8502**
**1-800-237-9083**

# THE FIRST NAME IN QUALITY CARE FOR THE BLACK HYPERTENSIVE

Once-daily 'Dyazide' gives your black patients, as well as your elderly patients, dependable blood pressure control. This plus decades of quality and experience all add up to the first-class care your hypertensive patients deserve.

**DYAZIDE®**
25 mg Hydrochlorothiazide/50 mg Triamterene/SKF

*The Original.*

a product of
**SK&F LAB CO.**
Cidra, P.R. 00639
© SK&F Lab Co., 1989

**DYAZIDE®**
**25 mg Hydrochlorothiazide/50 mg Triamterene/SKF**

*Before prescribing, see complete prescribing information in SK&F LAB CO. literature or PDR. The following is a brief summary.*

*Indications and Usage:* Hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone; in patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked.

This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

'Dyazide' may be used alone or as an adjunct to other antihypertensive drugs; dosage adjustments may be necessary.

*Contraindications:* Concomitant use with other potassium-sparing agents such as spironolactone or amiloride; potassium supplements (except in presence of severe hypokalemia); anuria, acute and chronic renal insufficiencies or significant renal impairment; hypersensitivity to drug or other sulfonamide-derived drugs; preexisting elevated serum potassium concentration.

*Warnings:* Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium-conserving diuretic combinations, including 'Dyazide'. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving 'Dyazide', when dosages are changed or with any illness that may influence renal function.

If hyperkalemia is suspected, obtain an ECG and monitor serum potassium. If hyperkalemia develops, discontinue 'Dyazide' and initiate thiazide therapy if needed. Persistent hyperkalemia may require dialysis. Monitor serum electrolytes frequently in patients with mild renal dysfunction and in diabetic patients. In patients who may develop respiratory or metabolic acidosis, monitor serum electrolytes and acid/base balance frequently.

*Precautions:* The bioavailability of the hydrochlorothiazide and triamterene components of 'Dyazide' is about 50% of the maximum obtainable with oral therapy. Theoretically, a patient transferred from therapy with hydrochlorothiazide with or without triamterene might show an increase in blood pressure, fluid retention, or change in serum potassium. Extensive clinical experience with 'Dyazide', however, suggests that these conditions have not been commonly observed in clinical practice. (See CLINICAL PHARMACOLOGY.) Use thiazides cautiously in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease; potassium depletion induced by the thiazide may be important in this connection; administer 'Dyazide' cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor; if mental confusion increases, discontinue 'Dyazide' for a few days; attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion. If patients develop hypokalemia, which is uncommon with 'Dyazide', increase potassium intake (i.e., with supplements or potassium-rich foods). If repeat determinations show serum potassium concentrations below 3.0 mEq/L, discontinue 'Dyazide' and initiate potassium chloride supplementation. Institute corrective measures cautiously and monitor serum potassium concentrations frequently, especially in patients receiving digitalis or those with a history of cardiac arrhythmias. Diuretics may aggravate existing electrolyte imbalances, especially at high dosages or in patients on salt-restricted diets. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Chloride replacement may be required in the treatment of metabolic acidosis. If dilutional hyponatremia develops, restrict water intake. In actual salt depletion, initiate sodium chloride replacement. Use 'Dyazide' cautiously in patients with a history of renal stone formation.

If hyperkalemia develops when treating for hypokalemia, take corrective measures. Also discontinue 'Dyazide' and, if appropriate, substitute a thiazide diuretic until potassium levels return to normal. Do periodic BUN and serum creatinine determinations, especially in the elderly and in patients with suspected or confirmed renal insufficiency. Serum PBI levels may decrease without signs of thyroid disturbance. Discontinue thiazides before conducting parathyroid function tests.

Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine; therefore use cautiously in patients undergoing surgery. Monitor electrolytes in patients taking amphotericin B, corticosteroids or corticotropin concomitantly. Thiazides may potentiate the action of other antihypertensive drugs. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be needed. 'Dyazide' may raise the level of blood uric acid; dosage adjustments of antigout medication may be needed to control hyperuricemia and gout. The following agents given with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq of potassium per liter of whole blood when stored for more than 19 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium), and salt substitutes (most contain substantial amounts of potassium). Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium concentrations by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake. Chronic or overuse of laxatives may reduce serum potassium concentrations by promoting excessive potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene. The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine. 'Dyazide' will interfere with the fluorescent measurement of quinidine.

There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Thiazides and triamterene cross the placental barrier and appear in cord blood. The use of thiazides in pregnancy requires weighing the anticipated benefit against possible hazards, including fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Thiazides appear, and triamterene may appear, in breast milk. If use of the drug is essential, the patient should stop nursing. Safety and effectiveness in children have not been established.

*Adverse Reactions:* The serious adverse effects associated with 'Dyazide' have commonly occurred in less than 0.1% of patients treated with this product. Anaphylaxis, rash, urticaria, photosensitivity, cardiac arrhythmias, postural hypotension, diabetes mellitus, hyperkalemia, hyperglycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia, jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain, acute renal failure, interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment, leukopenia, thrombocytopenia and purpura, megaloblastic anemia, muscle cramps, weakness, fatigue, dizziness, headache, dry mouth, impotence, sialadenitis. Thiazides alone have been shown to cause the following additional adverse reactions: paresthesias, vertigo, xanthopsia, transient blurred vision, allergic pneumonitis, pulmonary edema, respiratory distress, necrotizing vasculitis, exacerbation of lupus, aplastic anemia, agranulocytosis, hemolytic anemia. In neonates and infants: thrombocytopenia and pancreatitis—rarely, in newborns whose mothers have received thiazides during pregnancy.

*Supplied:* Capsules containing 25 mg hydrochlorothiazide and 50 mg triamterene, in bottles of 1000 capsules; in Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

BRS-DZ:L59
a product of
**SK&F LAB CO.**
Cidra, P.R. 00639
© SK&F Lab Co., 1989

Journal of the Arizona Medical Association

ARIZONA MEDICINE

June 1990, VOL. XLVII, No. 6

Marshall B. Block, M.D.

# To Save Medicine Or to Break Medicine: That is the Question!

Making morning hospital rounds is usually a hassle. Trying to find your patients or their charts or tracking down missing lab and/or radiological reports are usually sufficient morning stimuli that caffeine is not needed. Weekend rounding, although not desirable, is usually more leisurely accomplished since the pressure of getting to the office on time is missing. Therefore, one Sunday morning I spent a greater amount of time than usual talking about nothing in particular with an intelligent, sophisticated and medically knowledgeable patient. We talked about the gamut of changes that had taken place in medicine recently and the fact that everyone had an agenda of their own within the health care system. We discussed that this made it extremely difficult for groups to get together. He concluded by saying that, "No one is really out to save medicine, rather, everyone is out to make money from medicine." I have given that statement much thought and I have come to the conclusion that my patient's thought may not be far from the truth.

There are multiple players on the current health care scene, ranging from the practitioner in the trenches to the Chief Executive Officer on the 82nd floor, to our elected representatives locally and nationally. The common thread tying them together is, unfortunately, not the conservation of the essence of medicine, i.e., the trust between patient and physician but rather, their respective "bottom lines."

For instance, nationally we hear a great deal about the "R.B.R.V.S. System" for physician reimbursement which Medicare is currently embracing. Although this is an attempt at equalizing payment for physician services based on cognitive rather than on technical skills and as such has merit, is it really not a ploy to reduce the outcry that will occur when Medicare begins the ratcheting of reimbursement in general? Is the Health Care Financing Administration (H.C.F.A.) really interested in who gets what percentage of the pie? Isn't H.S.F.A. only concerned about the size of the pie? Controlling the burgeoning costs of medical care within the scope of our federal budget is what drives the bureaucracy and our legislators. Very few legislators have dealt with the larger issue of quality and access.

How about hospitals? Much has been written about their "non-profit status," but how many of them are in covert or overt competition for the "health care dollar"? The establishment of outpatient facilities of all sorts, the development of full time paid medical staffs to generate business for the hospital, and the establishment of "for-profit" hospital related enterprises don't seem destined to help our health care system as much

*(Continued on page 5)*

Journal of the Arizona Medical Association

ARIZONA MEDICINE

June 1990, VOL. XLVII, No. 6

*Arizona Medicine* is a socioeconomic and scientific journal published monthly by the Arizona Medical Association, Inc., 810 West Bethany Home Road, Phoenix, Arizona 85013, in conjunction with *The Western Journal of Medicine*. All views and opinions expressed in the articles published herein are the authors' and may or may not reflect those endorsed by the Arizona Medical Association.

(602) 246-8901 in Phoenix
1-800-482-3480 Statewide

Mark Ivey, Jr., M.D.
*President*

Chic Older
*Executive Vice President*

Marshall B. Block, M.D.
*Editor*

Susan Fuchs
*Director of Communications*

Gayle Mueller
*Publishing Coordinator*

Linda N. Brown
*Editorial Assistant*

Please notify publisher at least six weeks prior to change of address and include old and new address and a mailing label from most recent copy of *Arizona Medicine*. Include your new postal Zip Code number.

## In This Issue:

- **Failure to Thrive: The Plight of the Arizona Rural Hospital**
- **Physicians in the News**
- **Arizona Physicians Directory**

# From Our President

**Mark Ivey, Jr., M.D.**
**President, ArMA**

I can't believe the year is gone. I've spent 12 months telling people how important it is that the patient comes first, and how important it is for physicians to be proactive advocates for their patients. We've visited almost all the county medical societies in the state, many of the hospital medical staffs and various health care forums. We even went to Mexico to establish a relationship with our colleagues in Sonora, and discussed their local problems which are magnified by the tremendous influx of Americans. At home, the Association's staff structure was reorganized and new programs have been started for the benefit of our members.

During this past year, we have expanded our computer capabilities and developed an innovative electronic communications system for members of the Executive Committee, ArMA staff, Maricopa and Pima County Medical Society Presidents, with plans on the drawing board for further expansion. Our system has been recognized by the AMA as a prototype for the nation, not a shabby rating for a small state like Arizona. In other areas, we have expanded the services offered to members through ArMA's subsidiaries, ArMA Financial and ArMA Membership Benefits. ArMA Financial Services has IRAs and Keoghs, VEBAs and profit sharing plans and is managing more than $100 million worth of investments for our members; ArMA Membership Benefits has developed health, life and disability insurance programs designed specifically for the unique needs of physicians. We have negotiated a vehicle leasing system for members and have expanded our discount pager service program with U.S. West Paging. I am pleased to report that our historical project headed by John Kennedy, M.D., is successfully compiling an account of ArMA's establishment, development and activities through the years. Our public relations program has improved communications with the membership through a redesign and restructuring of our newsletter, Medical Memo, to make it more timely and more readable. Our communications with the public have been enhanced through expanded contact with the media.

Most importantly, we have reached out to physicians across Arizona to find out what they think we should be doing for them, and we have taken a solid look at the Association's activities to see how it can better meet those needs.

In short, it's been an incredibly busy time and we all should be exhausted. But we're not. We're inspired and full of energy and ready for another year of leaps forward.

It is imperative that we, as physicians, get involved politically so that we can put some brakes on the burgeoning bureaucratic intrusions by all levels of government into the practice of medicine, into the patient-physician relationship. I believe there is an answer to the problem of 37 million Americans who are uninsured, underinsured or uninsurable. The AMA 16-point plan is a foundation carefully structured to preserve the patient-

*(Continued on page 6)*

Recently, MICA conducted a survey of our policyholders to discover what questions they had about medical malpractice insurance. During the next few months, we'll respond to their questions.

# COMMONLY ASKED QUESTIONS ABOUT MEDICAL MALPRACTICE INSURANCE ANSWERED BY MICA

**What is MICA doing to reduce rates?**

Working in conjunction with organized medicine, MICA lobbied for the Periodic Payments Bill, which allows certain medical malpractice awards to be paid in installments rather than in lump sums. After it's passage in September of last year, MICA announced a 5% decrease in premiums for all of our policyholders.

MICA continues to monitor the frequency and severity of claims in our effort to reduce rates. In fact, MICA has received approval from the Department of Insurance to reduce rates by 13.8%, for new and renewal business effective April 1, 1990. Together these decreases will represent an 18.2% reduction in our rates within the last year.

Our efforts to screen out suit prone physicians, to handle claims efficiently and to encourage our policyholders' participation in risk management programs have all been effective as well. Our operating expense ratios are among the lowest in the industry.

We are also working for tort reform. We feel that tort reform is the only long term solution to reducing medical malpractice rates.

**What is MICA's new tail coverage program?**

MICA has received approval from the Department of Insurance that allows for tail credits – up to 50% discount off the tail premium. "Tail coverage" or an "extended reporting endorsement" protects physicians from claims resulting from situations that occurred while they were insured with MICA but that are not made until after their policies have expired. The credit can only be applied toward future tail purchase.

We can now offer our members a 5% tail premium reduction for each consecutive year of qualifying coverage with MICA. For example, if you are an active policyholder who has been covered for five years, you have already accumulated a 25% tail cost reduction. If you were previously insured with us, we will credit you for past qualifying years upon your return. Our unique program has no age restriction and does not require retirement from practice. The Tail Credit Program is an example of MICA's ongoing efforts to reduce medical malpractice insurance costs.

MICA hopes the answers to these commonly asked questions will help physicians better understand the complexities of medical malpractice insurance.

As a doctor-owned malpractice carrier – insuring more Arizona physicians than any other company – MICA's mission is to provide professional liability insurance at the lowest actuarially sound rates.

**MICA Mutual Insurance Company of Arizona**

To learn more call MICA: **(602) 956-5276** or Toll Free **(800) 352-0402.**

# Failure to Thrive: The Plight of the Arizona Rural Hospital

The 27 short-stay, non-federal, general hospitals located outside metropolitan Phoenix and Tucson are a vital component of the state's health care system. Fourteen have fewer than 50 beds and three have more than 100. They represent 46 percent of the state's hospitals and 17 percent of the total bed capacity. At least one hospital operates in every rural county with the exception of Greenlee.

These hospitals are experiencing declining occupancy rates, constrained income due to Medicare and other third-party reimbursement, small medical staffs, liability concerns, high levels of debt, and the leakage of patients to urban hospitals.

Hospitals are the mainstay of rural health systems. Public health programs and physicians depend on rural hospitals to carry out their professional responsibilities. They are usually the only source of emergency medical care especially for accidents resulting from hazardous occupations; they play a critical role in attracting physicians to rural areas; and they have, traditionally, been the major source of health care for many Arizonans.

Seven Arizona rural hospitals have ceased operating since 1979. The common variable shared by them, with the exception of one that was a hospital district, is that they were not community owned, operated, or financed. They were owned or operated by mining companies (5) or distant multi-hospital systems (1). The hospitals closed when the copper mines shut down or reduced activity or, in the case of the multi-hospital system, when too much money was being lost.

What is the impact of hospital closures on the populations they once served? The closure of any hospital clearly results in a reduction of accessibility to inpatient care, as measured by beds per capita. However, a better measure of access would adjust for differences in the health status of the population. If the distribution of rural hospital beds is not associated with health status, then occasionally closing a hospital may not reduce access in any meaningful way. In fact, elimination of unneeded rural hospitals would serve the policy objectives of regionalization.

It would appear that three points need to be addressed in the development of public policy that seeks to assure that rural communities secure or retain those hospital services they need. The three points are:

### Community Control

The hospital special tax district is the most direct mechanism for community control. Community control appears to be a key variable, only one of the seven hospitals that have ceased operating was a district.

### Planning/Regionalization

The determination of need for a hospital or hospital services should be agreed upon as a result of a broadly participative planning effort which includes consideration of the health status of the community residents, proximity of other hospital services, cost efficiency, potential utilization/acceptance, etc.

### Options for Different Types of Hospitals

Communities should have the option of addressing their inpatient needs by various means. Arizona offers only two general hospital licensing categories and the differences between them are not meaningful for communities looking for more cost-effective ways to provide hospital services. More varied licensing categories are needed.

In the opinion of some, rural Arizona will witness more hospital closures. They will be mainly for economic reasons resulting from declining occupancy and restricted reimbursement. We must all share the responsibility for assuring that future closures do not result in unacceptable risks to the health status of the residents. ■

**Phillip M. Lopes,**
**Assistant Director**
**Rural Health Office**
**Department of Family and Community Medicine**
**College of Medicine,**
**University of Arizona**

# To Save or Break Medicine

*(Continued from page 1)*

as the health of the institution itself. Are hospitals out to "save medicine" or *themselves?*

Corporate America with its millions of workers is searching for ways to control health care costs by limiting access or controlling quantity. They are concerned with their own profits and, unfortunately, they answer to a higher authority, their shareholders rather than their workers. Some day they too will have to face quality issues and rationing decisions which they, heretofore, have avoided or have relegated to others.

University and medical school leadership should be in the forefront of trying to develop a system which will be able to distill the best and bottle it in a more palatable form. The "novel approaches" to health care cost, health care delivery, and health care review are actually experiments performed by social scientists, be they physicians, economists or political scientists. Are not these funded researchers conducting major social experiments with our health care system, much as they would conduct any other experiment without knowing the ultimate result? Is this not a chancy way to change our system and the health of our nation? Unfortunately, with the increasing costs for medical education and the shrinking funds to support it, medical school leadership's view has also narrowed. They too appear to be more concerned with their own existence than with that of our country's health and welfare.

As physicians, are *we* interested in "saving medicine?" How many of us applaud the increasing scrutiny both federally (the P.R.O.) and locally (BOMEX) which has for the most part improved the quality of care to our patients? How many complain when our charts are reviewed but don't offer to become involved in the process in order to make it more effective? How often do we ask, "Will this procedure or test offer any advantage to a patient's management, *before* ordering it?

What about our patients? One would think that the elderly who have experienced the advantages as well as the disadvantages of the past thirty years of medicine would want to salvage portions of our system which they perceive as good. Yet, they are vociferous only when it comes to matters of money, i.e., either because we as a nation are spending too much on health care or we are not offering enough, i.e., we are attempting to ration care or we as physicians are charging too much! They do not want us to limit services, yet they complain when we tax them in order to be able to provide additional care. They seem more interested in their own health than that of our health care system!

Yes, my patient's view may not be that far off the mark! Each of the players, be they patients, hospitals, insurance companies, corporations or practitioners have their own agenda, that of self survival. Who is it that is looking after the survival of our health care system? Who of these players is going to rise up and look beyond their own parochial interestes in order to weed out what is good and discard that which is superfluous? As physicians we recognize that the basis of medical care is the trust that is developed between the patient and his or her physician. Although some of us may have the vision to rise above and take the reigns, the vast majority of us must be content to guard this crucial essence of what is called medicine. We must remember that we, of all the players in the health care system, are the only ones who continue to carry a "black bag" rather than a briefcase.

**Marshall B. Block, M.D., Editor**

## To the Editor:

It was gratifying to note the article "HIV Blood Test Counseling" in your March 1990 issue. Public health officials of course have a strong interest in seeing that physicians and other health professionals render comprehensive and sensitive pre-and post-test HIV counseling to individuals seeking HIV testing. Even with recent advances in therapy relating to HIV infection and opportunistic infections, it is still quite clear that education and behavior change are the main weapons in the strategy against further HIV transmission, and proper edcuational counseling can greatly contribute towards this strategy.

To supplement this article, several additional details pertinent to Arizona physicians should be noted. First, physicians should be aware that additional HIV counseling guidelines are available in the Arizona Medical Association's Position Statement on AIDS, published January 1988. Also, physicians should be aware that county health departments can play a key role in the HIV counseling and testing process. Anonymous testing is available through county health departments; some patients may prefer to receive anonymous testing through the health department, rather than confidential testing through their physician's office.

In addition, patients who test positive can receive assistance in confidential notification of sexual and/or needle-sharing partners by trained county health department personnel. This service may be requested by either the physician or the patient.

Again, please accept my thanks for providing important information regarding HIV counseling and testing.

**Steven J. Englender, M.D., M.P.H.**
**Assistant Director**
**Arizona Department of Health Services**

## From Our President

*(Continued from page 2)*
physician relationship while allowing the free enterprise system to continue to give the individual a choice.

I have personally been, and will continue to be, politically active, to do my part to work toward these goals. There are political battles at all levels to be waged, battles on the local level, at the state legislature and especially in Washington, D.C. At all these levels, it is imperative that we work with one guiding principle: ***whatever we do, everything we do, must be structured toward putting the patient first.***

Mark Ivey Jr., M.D., President


**MEDICAL BOOKSTORE**

**MEDICAL BOOKSTORE**
College of Medicine
Arizona Health Sciences Center
Tucson, Arizona 85724
Phone: 626-6669


**Arizona Medical Association**

**99th Annual Meeting**

**June 7, 8 & 9**

**Wyndham Paradise Valley Resort**

**Scottsdale**

# PUT YOUR MEDICAL CAREER IN FLIGHT.

Discover the thrill of flying, the end of office overhead and the enjoyment of a general practice as an Air Force flight surgeon. Talk to an Air Force medical program manager about the tremendous benefits of being an Air Force medical officer:

- Quality lifestyle, quality practice
- 30 days vacation with pay per year
- Support of skilled professionals
- Non-contributing retirement plan if qualified

Discover how to take flight as an Air Force flight surgeon. Talk to the Air Force medical team today. Call

**USAF HEALTH PROFESSIONS**
**TOLL FREE**
**1-800-423-USAF**

AIR FORCE

# Physicians in the News

Paul Hanson, M.D.

**Paul Hanson, M.D.**, has been named admitting/attending physician at Remuda Ranch Center for Anorexia and Bulimia in Wickenburg. He is responsible for the implementation of medical care, admitting evaluations and treatment plans for all patients at the facility.

He has been a solo practitioner in internal medicine for the past five years at Wickenburg Community Hospital. Before moving to Wickenburg, he practiced internal medicine and consultation at Squaw Peak Medical Clinic in Phoenix.

Dr. Hanson is an active member of the American College of Physicians and his board certification in internal medicine is pending. Additionally, he served on St. Joseph's Internal Medicine Residency Selection Committee, Humana Hospital (Phoenix) Critical Care and Patient Care Board and St. Joseph's Hospital Medical Education Committee.

He received his B.S. degree from Northern Arizona University and his medical degree in 1978 from Arizona State University.

**Jack A. Friedland, M.D.**, was elected president of the American Society for Aesthetic Plastic Surgery during the 23rd Annual Scientific Meeting held April 1-6 in Chicago. The society is comprised of nearly 900 board certified physicians concentrating in aesthetic surgery.

Dr. Friedland is certified by the American Board of Plastic Surgery.

Jack A. Friedland, M.D.

His hospital appointments include St. Joseph's Hospital and Medical Center, Good Samaritan Hospital, Phoenix Children's Hospital, St. Luke's Hospital and Medical Center, and Scottsdale Memorial Hospital. He has served as chief of surgery at St. Luke's Hospital, chief of plastic surgery at Phoenix Children's Hospital and is past president of the medical staff of Children's Rehabilitative Services.

He received his medical degree from Northwestern University Medical School in 1965. His surgical internship and residency were at New York University-Bellevue Medical Center in New York. He took his plastic surgery residency at the Institute of Reconstructive Plastic Surgery, New York University Medical Center.

For the past 15 years Dr. Friedland has been a sole practitioner of plastic surgery in Phoenix.

Tucson pathologist, **Ronald Spark, M.D.**, has been elected secretary-treasurer of the National Association of Physician Broadcasters (NAPB). He is a co-founder and charter board member of NAPB, an association of mediadocs. The NAPB membership includes such well-known physicians as Red Duke, Dean Edell and C. Everett Koop.

Ronald Spark, M.D.

Dr. Spark began his involvement with the broadcasting media in 1980 when he initiated the radio program "Prescription forHealth" on Tucson station KTUC. This program was the first Arizona-originated radio show providing health and medical information. Since 1984 Dr. Spark has expanded his media involvement as moderator-writer for "Prescription for Health" which is aired on Tucson's cable TV network.

He says the purpose of the cable television program is three-fold:

- to feature physicians as caring, interested and interesting people;
- to give our philosophy of medical practice before the public in an interesting and entertaining format.

Dr. Spark said he has been fortunate to have Connie Wry as both producer and director of the cable television show.

For outstanding contributions in the media, Dr. Spark has received both the Orchid Award from the Tucson Press Club and the Oasis Award for series excellence from the Tucson Community Cable Corporation.

Dr. Spark has been a pathologist in Tucson since 1974. Prior to that he served in the U.S. Army Medical Corps.

---

Two valley physicians have received three year appointments as Cancer Liaison Physicians from the Commission on Cancer. **Patrick J. Donovan, M.D.** of Scottsdale will serve Scottsdale Memorial Hospital and **Kent Zimmerman, M.D.**, of Mesa, will represent Desert Samaritan Hospital.

These doctors are part of a national network of 2,300 volunteer Cancer Liaison Physicians who provide leadership and support to the Hospital Cancer Program, and other Commission on Cancer activities. This program is an integral part of the Commission on Cancer of the American College of Surgeons.

**Patrick J. Donovan, M.D.**

**Kent Zimmerman, M.D.**

The Commission on Cancer has approved more than 1,200 cancer programs in hospitals across the country. There are seven approved cancer centers in Arizona, five in the metro-Phoenix area and two in Tucson. The Commission reviews each hospital's cancer program for conformity to standards set by the Commission and encourages participating hospitals to equip and staff themselves so they are able to provide the best in the diagnosis and treatment of cancer.

One of the major responsibilities of the Cancer Liaison Physician is providing support and technical expertise to the hospital's tumor registry program. All patients diagnosed with cancer or who are receiving treatment for cancer will be listed in the registry. The goal is to first gather the facts about cancer patients in each hospital to determine the type of cancer, how it was treated, what was the outcome and other pertinent facts. This information is disbursed to hospitals to aid in improving cancer patient care.

Dr. Donovan is board certified in internal medicine with sub-specialties in hematology and oncology. For the past four years he has been the Chairman of the Cancer Care Committee at Scottsdale Memorial Hospital. He is a member of the Southwest Oncology Group and affiliated with the University of Arizona Cancer Center.

Dr. Donovan received his medical degree from the University of Nebraska in 1977. He did a fellowship at the University of California San Francisco Cancer Research Institute in Medical Oncology and Hematology. In 1983 he moved to Arizona where he joined Scottsdale Medical Specialists.

Dr. Zimmerman is the medical director of Sonora Laboratory Sciences, Inc., Cytology Department. Sonora Laboratory is the only accredited laboratory in Arizona and one of 65 accredited laboratories nationwide. The accreditation is a professional honor given to cytology labs meeting high-quality standards, based on a thorough inspection of safety, procedures, equipment, and qualifications and working environment of laboratory personnel.

He earned his medical degree from the University of Iowa in 1978 and did his pathology residency at the University of Arizona. Dr. Zimmerman is board certified in pathology. In November, 1989 he became one of three in Arizona to pass the board examination for a sub-specialty in cytopathology. For the past three years he has served as the chairman of the Cancer Care Committee at Desert Samaritan Hospital in Mesa. ■

## HEALTHCARE DIAGNOSTICS MANAGEMENT
### Imaging Division, Tempe, Arizona

If you are considering providing diagnostic imaging services in your private office or specialty clinic and you're not sure where to start—then Healthcare Diagnostics Management (HDM) can be of assistance. HDM provides a complete range of diagnostic imaging management consulting services:

- **Short & Long Range Capital Assets Planning Including:**
  - Needs Assessment & Service Planning
  - Proforma & Financial Analysis / Feasibility Studies
  - Financing-Joint Venture Structures / Lease / Purchase
- **Imaging Systems Acquisition Services including:**
  - RFP (Administrative & Technical Purchase Specifications)
  - Vendor Bid Matrix & Analysis
  - Purchase & Maintenance Contract Negotiations
  - Acceptance Testing (Administrative & Engineering)
  - Used Imaging Systems Brokerage Services
- **Site Planning & Installation Preparation Services including:**
  - Imaging Facility Layout & Design
  - Imaging Systems Installation Requirements
  - Site Renovation or New Construction Oversight
- **New Service Implementation & Startup Including:**
  - Film Processor & Accessories Purchasing
  - Charge Structure Development & CPT-4 Coding
  - Quality Control Program & Technical Assistance
  - Practice Management Services
  - Bottom Line Analysis

Call Dan Maddox, President (602) 838-0423 for an appointment to discuss your needs.

## ARIZONA STATE GOVERNMENT PRISON PSYCHIATRISTS

Opportunity to work with a disadvantaged population. Seeking candidates for positions in Arizona State Prisons at: Florence (halfway between Phoenix and Tucson); Perryville (West of Phoenix); Wilmot (South of Tucson).

Salary range: $56,680 - $101, 961 + excellent benefits.

**WE PAY MALPRACTICE/TAIL**

**Phone/send resume to:**

**Mira Stewart**
**Medical Recruiter**
**Arizona State Personnel**
**1831 West Jefferson**
**Phoenix, AZ 85007**
**(602) 542-5482, M - F, 8 - 4**

Will return calls any time at residence, if requested. Utmost discretion observed.

# WHITE WATER

**$79** Per person plus tax

10 miles with lunch. Great idea for family, staff, and clients.

**461-9494**

***SALT RIVER CANYON WHITE WATER RAFTING***

# Classified Advertising


**WE WILL BIND YOUR PERIODICALS**

Preserve your medical journals as beautifully bound books. Choose om 24 colors of durable Library Buckram.

**$16.50 Per Volume**
**$20.00 Imitation Leather**
Name imprints (spine) $2.00
Decorative rules $1.00 each

Scattered ad removal $5.00 per volume

Inquire about quantity discounts. Free local pickup and delivery on rders of $250 or more. Minimum order is $35.00.

**ROSWELL BOOKBINDING**
**2614 North 29th Avenue**
**Phoenix, Arizona 85009 ● (602) 272-9338**

PHYSICIAN OFFICE LABORATORY TESTING is on the rise because it leads to increased medical practice efficiency by providing:

- Better patient care
- Increased patient/physician convenience
- Rapid test results for faster diagnosis and treatment

Let ASSOCIATED LABORATORY CONSULTANTS assist you in:

- Reimbursement maximization (proper CPT usage)
- Optimizing your existing laboratory
- Developing a new laboratory

Call 990-0068 for an appointment to discuss your needs.

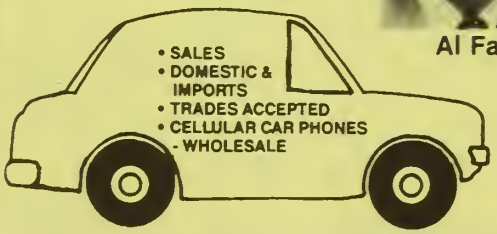
Associated Laboratory Consultants, Inc.,
Scottsdale, Arizona

**DANNY T. SEIVERT INSURANCE, INC.**
Professional Programs
for Professional People
70 E. Mitchell Dr., Suite 6
Phoenix, Arizona 85012
263-9090

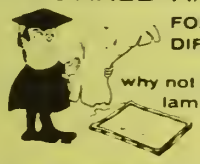
**CONSUMER AUTO BROKERS**
444 W. Camelback, Ste. 203
Phoenix 85013
274-4400

**A Personalized Car Buying Service**

Al Fann




YOU WORKED HARD



FOR THAT DIPLOMA
why not have it laminated?

it will last a lifetime....

**THE PLAQUE SHOP**

Wood plaques — Ready to hang
No glass to break — Moisture proof
Dirt proof -- Impressive.
Our plaques are manufactured locally

ARIZONA LAMINATING SERVICE, INC.
7231 East First Avenue
Scottsdale, Arizona 85251
(602) 945-9338

## *Professional Opportunities*

### Family Practitioner, BC/BE

To start a comprehensive clinic in Cottonwood, Arizona. Guaranteed salary, plus 50% of all clinic income over and above the salary after expenses, plus malpractice insurance and many other benefits. Contact Josephine Hayes, P.O. Box 421, Cottonwood, AZ 86326, (602) 634-0023.

### Practices Available

Allergy-Clinical immunology. Retiring by year-end. Established 40 years. Skin and original blood tests for solving clinical failures. Both non and immune cases due to food, liquids, oils, dyes, chemicals, medication, vitamins, inhalants, pollen, etc. Many cases are headaches, joint pain, skin, asthma, and depression. Diabetics reduce blood sugar about one half. Even lupus and M.S. regress. Trained staff. Total price is equipment. Also have teaching course 1 or 2 weeks. 233-D, 550 W. Thomas Road, Phoenix, AZ 85013.

### Director, Adolescent Treatment

Will administer adolescent treatment program. Duties include: analyzing community's needs, designing a clinical approach to meeting those needs, & recruiting a medical staff to implement design. Will supervise professional staff. Will coordinate the medical & psychiatric staff, & will coordinate the program with social workers, teachers & parents of patients. Requirements: M.D. Degree required with advanced training in a combination of Pediatrics & Psychiatry in addition, or which includes at least six months experience in the psychiatric care of adolescents. No license required. $60,000 per year/40 hr. wk. Job location: Yuma, Arizona. Qualified applicants send resumes by June 25, 1990 to: Arizona Western Medical Center, Attn: N.J. Wilson, M.D., 2149 W. 24th Street., Yuma, AZ 85364. Proof of authorization to work in U.S. required if hired. Equal Opportunity Employer.

### Hemorrhoids?

The Bad News: Other disorders (including cancer) can be confused with hemorrhoids. Don't self-treat. A careful examination is called for.

The Good News: You can avoid hospitalization and traditional hemorrhoid surgery. Your hemorrhoids can now be removed with one of our office procedures. Be back to work the next day. Stop in for a brochure giving details.

**The Baker Clinic**
**John Q. Baker, M.D.**
**Board Certified General Surgeon**
**In Edwards Professional Park**
**North 89th Place, just off Shea Blvd.**

### Radiologist Practice

Lucrative practice opportunity for radiologist who enjoys rural lifestyle. Excellent hospital, peer association and quality of life. Competitive start up malpractice, relocation reimbursement and more! Please call Lonnie Belden collect at (719) 637-4322 or write to E.G. Todd Associates, 1670 North Newport Road, Suite 300D, Colorado Springs, CO 80916.

### Internist Practice

Lucrative practice opportunity for internist who enjoys rural lifestyle. Excellent hospital, peer association and quality of life. Competitive start up compensation package including an income guarantee, malpractice, relocation reimbursement and more! Please call Lonnie Belden collect at (719) 637-4322 or write to E.G. Todd Associates, 1670 North Newport Road, Suite 300D, Colorado Springs, CO 80916.

### Orthopaedic Practice

If you are interested in a lucrative orthopaedic practice in a well managed, up-to-date hospital, a qualified and supportive medical staff, and a competitive start up compensation package, please call Lonnie Belden collect at (719) 637-4322 or write to E.G. Todd Associates, 1670 North Newport Road, Suite 300D, Colorado Springs, CO 80916.

### Family Practice, Radiology OB/GYN

Internal Medicine and other specialties needed for small to mid-sized towns in New Mexico and other Sunbelt and Inter-mountain states. Excellent facilities and competitive remuneration packages combine with good schools, outdoor recreation and beautiful locations to provide a quality lifestyle. All inquiries are fully confidential. Call Phyllis or Bruce Moffitt at (505) 898-1114 or send CV to CPS, PO 1163, Corrales, N.M. 87048.

### Phoenix Area

Behavioral Health Program seeking additional adult psychiatrist. Center provides child through adult inpatient, outpatient and partial hospitalization, adult and adolescent CD. Fee-for-services with shared call, or association with existing staff are options. Hospital provides competitive financial support. For more information, call Greg Peterson, E.G. Todd Associates, at (800) 776-7330 or collect (913) 341-7806.

### Locum Tenens Service

Radiologists available for locum tenens or permanent positions. Western Physicians Registry will provide whatever coverage you need for less. Please call Carol Sweig, director, (800) 437-7676.

## *Medical Office Space*

### Medical Office For Rent

32nd Street near Osborn. 1350 square feet. Ready to move in. $13 per square foot. 3427 N. 32nd St. Call Evelyn. (602) 956-0959

### Doctor - Doctor

Prime westside location. Freshly decorated, excellent parking, easy freeway access, security gates, 2300-3100 square feet available. Lease terms negotiable. Call (602) 839-0137.

## *Real Estate*

### Telluride Condo

For sale—3 bedrooms, 2 baths, cathedral ceilings, fully furnished, wood burning stove, walking distance to lift and village. Call (602) 790-6200 — ask for Irma.

### Phoenix Country Club Estate 131 East Country Club Drive

This mission monterey, originally built in 1929, has been beautifully restored and totally updated. Warmth, character and charm are evident throughout this property. This 4,754 square foot four bedroom, six bath, family room plus library home is perfect for a professional. This unique property MUST BE SOLD! $595,000. Prudential Arizona Realty, Jeannine Mills/Nancy U'Ren (602) 954-6888.

## *Miscellaneous*

### Physician Signature Loans

Loans to $50,000. Competitive fixed rates. No collateral. Up to seven years to repay with no pre-payment penalties. Prompt, courteous service. Physicians Service Association, Atlanta, Georgia. (800) 241-6905. Serving MDs for over ten years.

### Large Loans

Since 1966 specializing in large loans to physicians nationwide from $15,000 to $90,000. Long repayment terms at fixed interest rates. Commitments usually within 48 hours. Woodside Capital Corp., Woodside Capital Building, P.O. Box 368, Woodland Hills, CA 91365. For further information, call (800) 423-5025.

### Lab Equipment for Sale

Hemow Cell-counter, Lyte Tek, Coagulation Unimeter 500, Thyrotek. Call (602) 274-6055.

### For Sale

EEG machine. 10 channel Nihon Kohden. One year old. Like new. Accessories included. Price negotiable. Call Ann (602) 946-4263.

Clinical Investigation

# Misdiagnosing Ventricular Tachycardia in Patients With Underlying Conduction Disease and Similar Sinus and Tachycardia Morphologies

BLAIR D. HALPERIN, MD, *Denver;* JACK KRON, MD, *and* JOEL E. CUTLER, MD, *Portland;*
PETER J. KUDENCHUK, MD, *Seattle;* JOHN H. McANULTY, *Portland*

*Six patients presented with wide-complex tachycardias with QRS morphologies similar to those seen on their electrocardiograms that showed normal sinus rhythms. During normal sinus rhythm, each patient had an underlying intraventricular conduction abnormality or bundle branch block. Despite the similarity of the QRS complexes to those seen during sinus rhythm, the tachycardias subsequently proved to be ventricular in origin in each patient. It is important not to misdiagnose these disorders as supraventricular tachycardia as an erroneous diagnosis may result in inappropriate management.*

(Halperin BD, Kron J, Cutler JE, et al: Misdiagnosing ventricular tachycardia in patients with underlying conduction disease and similar sinus and tachycardia morphologies. West J Med 1990 Jun; 152:677-682)

A tachycardia showing wide QRS complexes on electrocardiograms (ECGs) can be ventricular or supraventricular in origin. The misdiagnosis and mistreatment of ventricular tachycardia as supraventricular tachycardia, or vice versa, can result in deleterious outcomes. Several authors have proposed electrocardiographic criteria for ventricular tachycardia based on QRS width, configuration, axis, and, most important, the presence or absence of atrioventricular or ventricular His dissociation.[1-4] Interpretation can be difficult even when these criteria are used. One confounding variable is the presence of an underlying bundle branch block on the ECG showing sinus rhythm. A comparison of QRS complexes during tachycardia and sinus rhythm has been proposed to address this problem. Identical QRS morphologies on ECGs showing sinus rhythm and those showing arrhythmia suggest a supraventricular origin, and dissimilar morphologies suggest a ventricular origin. The six patients we present in this report had ventricular tachycardia, but the QRS morphologies during the arrhythmias were similar to those observed during normal sinus rhythm when each had an intraventricular conduction delay.

## Report of Cases

### *Case 1*

The patient, a 71-year-old man, showed sinus rhythm, anterior and inferior Q waves, and right bundle branch block with right axis deviation on a resting electrocardiogram in 1983. In 1987 he experienced an episode of lightheadedness and chest pain and was noted to be in a wide-complex tachycardia, at a rate of 160 beats per minute, that required cardioversion. Similarities in 12-lead ECG morphology and axis during the tachycardia and sinus rhythm did not allow a differentiation between ventricular and supraventricular origins (Figure 1). Electrophysiologic testing showed atrioventricular dissociation and documented ventricular tachycardia with no His bundle potential before the QRS complexes.

### *Case 2*

The patient, a 61-year-old man with a remote history of an anterior myocardial infarction, had recurrent symptomatic wide-complex tachycardia with features similar to those seen on a resting 12-lead ECG (Figure 2). Both tracings showed a QRS morphology consistent with right bundle branch block, left anterior fascicular block, and an old anterior myocardial infarction. The rhythm was initially diagnosed as supraventricular in origin and was treated with a regimen of verapamil hydrochloride and later propranolol hydrochloride. Electrophysiologic testing proved this tachycardia to be ventricular in origin, with 1:1 ventricular-to-atrial conduction through the normal conduction system with a sequence of ventricular to His bundle to atrial activation.

### *Case 3*

Lightheadedness and chest pain developed in 1988 in a 77-year-old man with an old anteroseptal myocardial infarction. A rhythm strip at that time showed a wide QRS complex tachycardia that converted to sinus rhythm during a lidocaine infusion. The resting ECG revealed sinus rhythm with right bundle branch block, left anterior fascicular block, and an old anteroseptal myocardial infarction. Subsequent programmed electrical stimulation induced a ventricular tachycardia with ventricular-to-atrial dissociation and no evidence of His activity before each QRS complex. The morphology was similar to that seen during sinus rhythm (Figure 3).

From the Department of Medicine, Division of Cardiology, University of Colorado Health Sciences Center, Denver (Dr Halperin); the Department of Medicine, Division of Cardiology, Oregon Health Sciences University School of Medicine, Portland (Drs Kron, Cutler, and McAnulty); and the Division of Cardiology, Harborview Medical Center, Seattle (Dr Kudenchuk).

Reprint requests to Jack Kron, MD, Division of Cardiology, L462, Oregon Health Sciences University, 3181 SW Sam Jackson Park Rd, Portland, OR 97201.

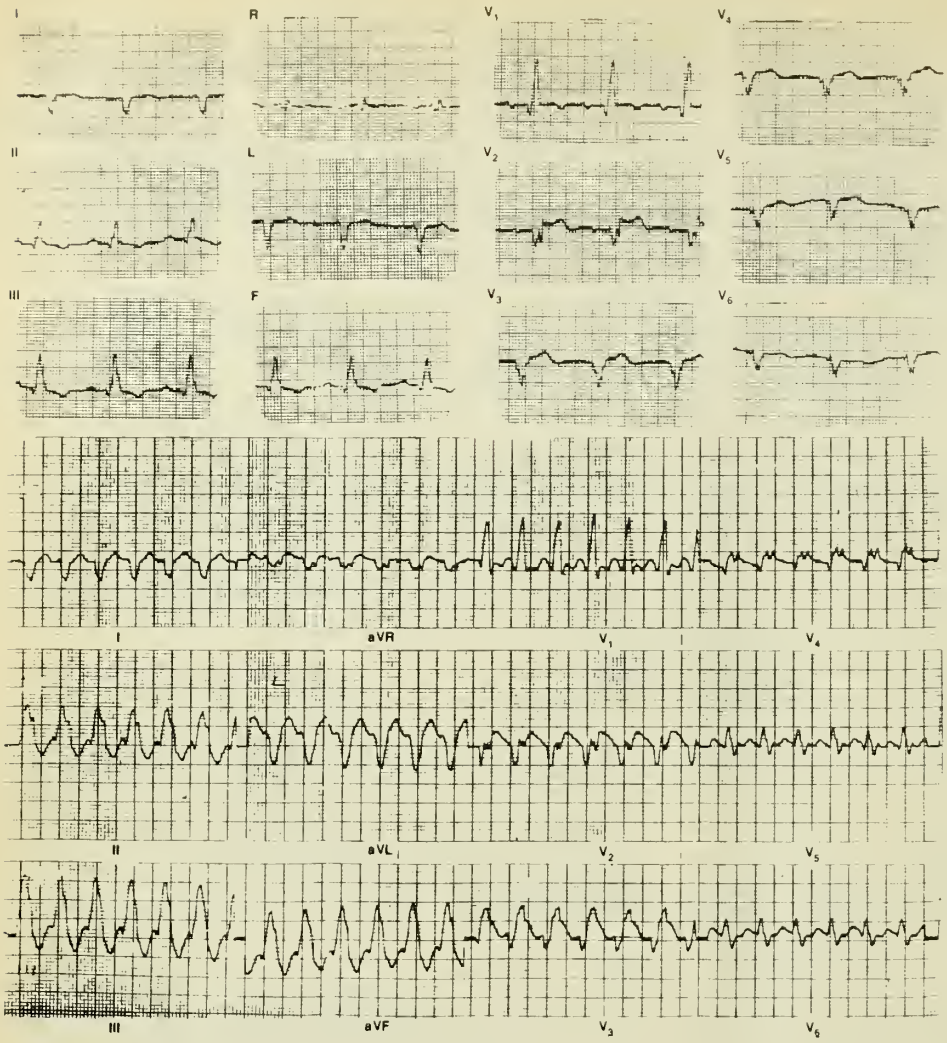



**Figure 1.**—The electrocardiograms show sinus rhythm **(top)** and ventricular tachycardia **(bottom)** in a 71-year-old man with wide-complex tachycardia. Note the loss of Q waves inferiorly during ventricular tachycardia.

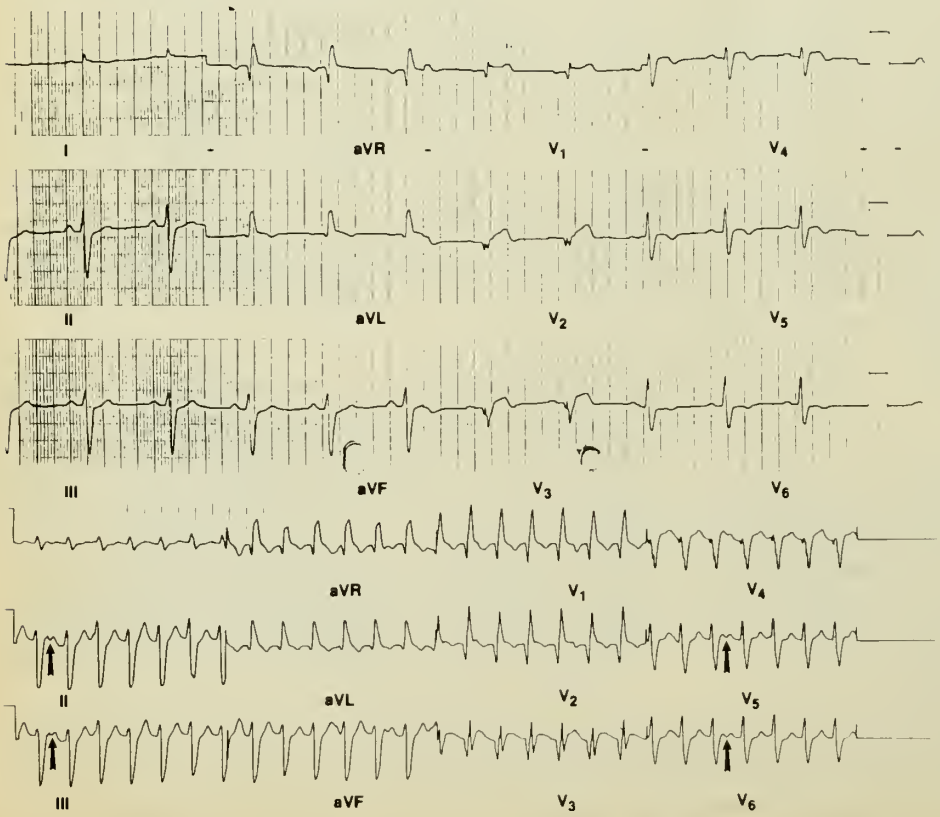



**Figure 2.**—The electrocardiograms show sinus rhythm **(top)** and tachycardia **(bottom)** in a 61-year-old man with a previous anterior myocardial infarction. The arrows signify possible P waves, which favor the diagnosis of ventricular tachycardia.

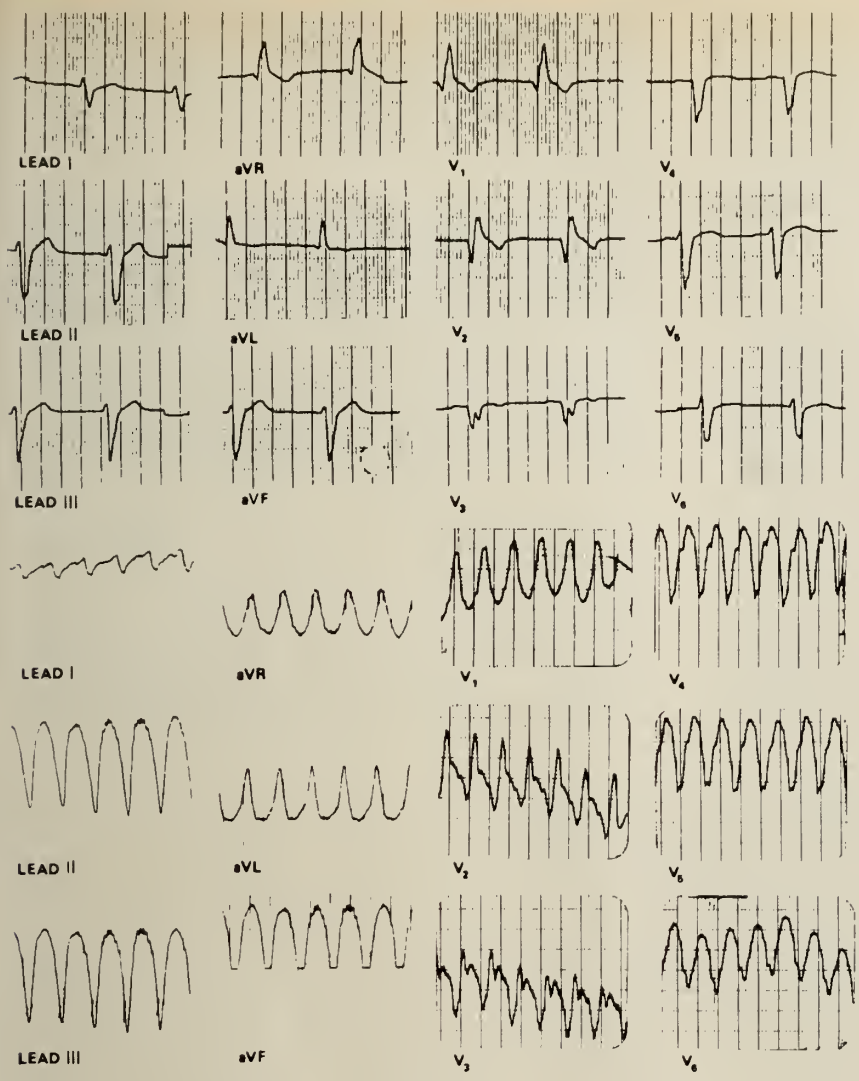



**Figure 3.**—The electrocardiograms show sinus rhythm **(top)** and tachycardia **(bottom)** in a 77-year-old man with a previous anteroseptal myocardial infarction and new occurrence of a wide-complex tachycardia. Note the loss of small R waves in the inferior leads during the tachycardia, which was associated with a slight widening of the QRS complexes.

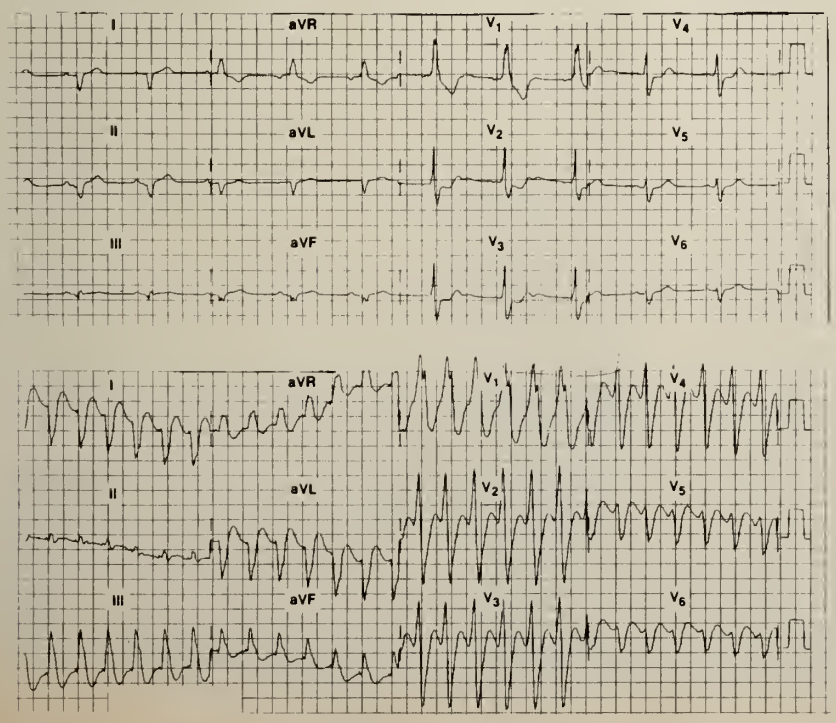



**Figure 4.**—Electrocardiograms were taken during sinus rhythm **(top)** and ventricular tachycardia **(bottom)** in a 56-year-old man with a previous bypass operation. During ventricular tachycardia there is an axis shift associated with widening of the QRS complexes, although the morphologies of the rhythms are similar.

*Case 4*

In this patient, a 56-year-old man with previous myocardial infarctions and a coronary artery bypass operation, a wide-complex tachycardia developed that required cardioversion before a 12-lead tracing could be recorded. During a subsequent electrophysiologic study, induced ventricular tachycardia has a morphology similar to that seen during sinus rhythm (Figure 4).

*Case 5*

The patient, an 82-year-old woman with a remote inferior wall myocardial infarction, had several recurrent episodes of tachycardia with wide QRS complexes for which she had been treated with a regimen of verapamil, digoxin, and disopyramide phosphate. After an episode of ventricular fibrillation, she had inducible ventricular tachycardia similar in morphology to that seen on her resting 12-lead ECG (Figure 5).

*Case 6*

A 61-year-old man with a previous inferior wall myocardial infarction had an intraventricular conduction delay with a QRS width of 0.10 seconds on his sinus rhythm ECG. He had recurrent episodes of symptomatic tachycardias, some of which showed a QRS complex that was the same as that occurring in sinus rhythm, except that it lasted 0.12 seconds. Atrioventricular dissociation was seen on the ECG (Figure 6) and by intra-atrial recordings.

## Discussion

In patients with intraventricular conduction abnormalities, physicians should consider a tachycardia that elicits wide QRS complexes to be ventricular until proved otherwise. These patients with an underlying conduction disturbance and a QRS morphology during ventricular tachycardia that is remarkably similar to that seen during sinus rhythm illustrated the importance of this rule. A similar QRS morphology during tachycardia does not always mean that it is supraventricular in origin. The accurate diagnosis of ventricular tachycardia is of paramount importance because misdiagnosis frequently results in inappropriate management.[5,6]

In many patients who present with a wide-complex tachycardia, a systematic approach to interpreting the electrocardiogram results in the correct diagnosis.[1-4,7-10] Clues favoring ventricular tachycardia include evidence of atrioventricular dissociation, a QRS width greater than 140 milliseconds, a left or unusual axis, and the presence of fusion beats.[4] Most of these criteria were derived from patients who had a

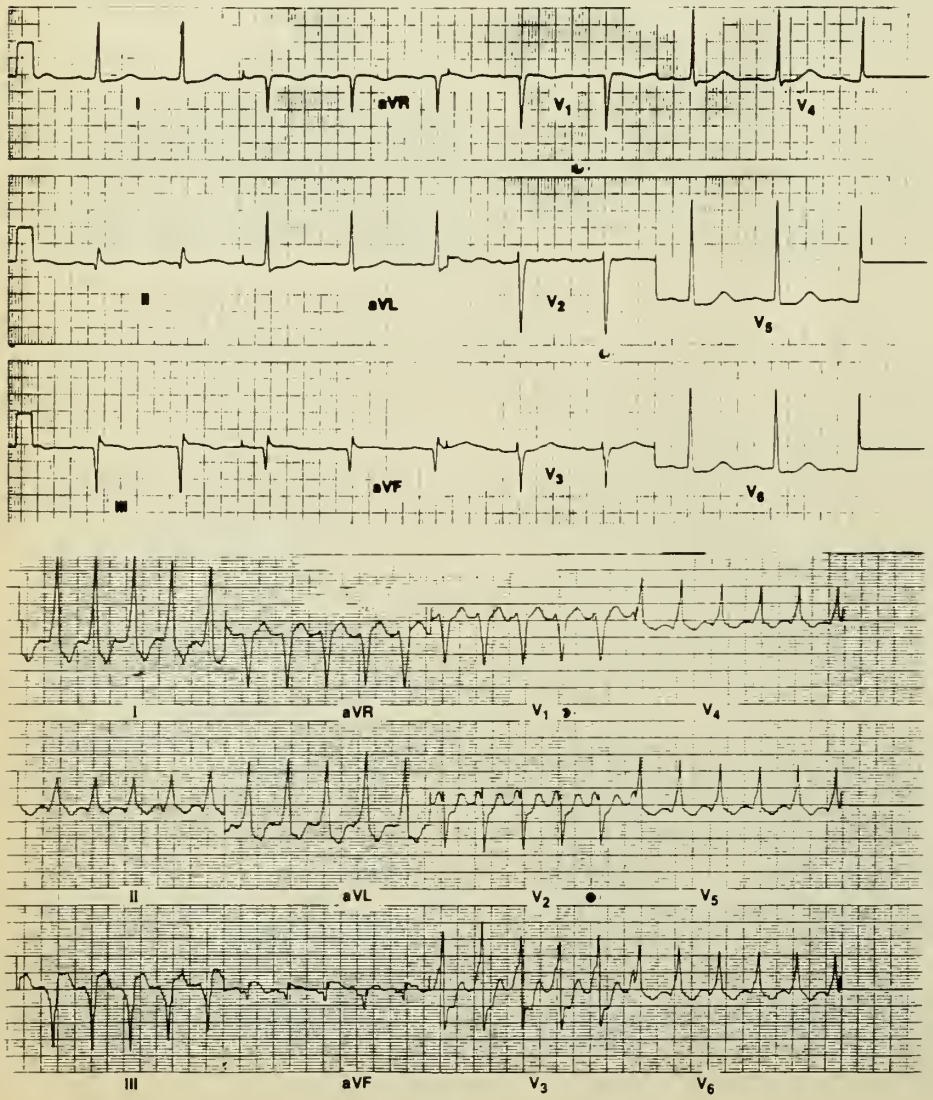



**Figure 5.**—Electrocardiograms were taken during sinus rhythm **(top)** and ventricular tachycardia **(bottom)** in a 82-year-old woman with a previous inferior myocardial infarction and borderline intraventricular conduction delay during sinus rhythm. Except for a widening of the QRS complexes during ventricular tachycardia, the electrocardiograms remain identical.

normal QRS duration on their sinus rhythm ECG. Therefore, as noted by those who established the rules, the criteria may not apply to patients with underlying conduction disturbance. Furthermore, the effects of antiarrhythmic drug therapy on tachycardia morphology and duration may further limit these criteria.

Dongas and co-workers recently showed that in patients with underlying bundle branch block, there are frequently subtle differences in QRS morphology and duration on the 12-lead ECG that facilitate the correct diagnosis in the majority of patients.[7] During ventricular tachycardia, most patients they evaluated had a QRS complex that was longer by a mean of 56 milliseconds than that seen during sinus rhythm.

Kindwall and colleagues reported that during tachycardia with an appearance of left bundle branch block, a combination of four morphologic criteria correctly leads to the diagnosis of ventricular tachycardia in most cases.[8] These criteria include an R wave in $V_1$ or $V_2$ of longer than 30 milliseconds, any Q wave in $V_6$, a time span of longer than 60 milliseconds from the beginning of the QRS to the S wave nadir in $V_1$ or $V_2$, and notching on the S wave downstroke in $V_1$ or $V_2$. Most patients in their study had relatively normal conduction on their 12-lead ECGs that showed sinus rhythm. The authors cautioned that these criteria would probably not apply to patients with underlying left bundle branch block who presented with supraventricular tachycardia.

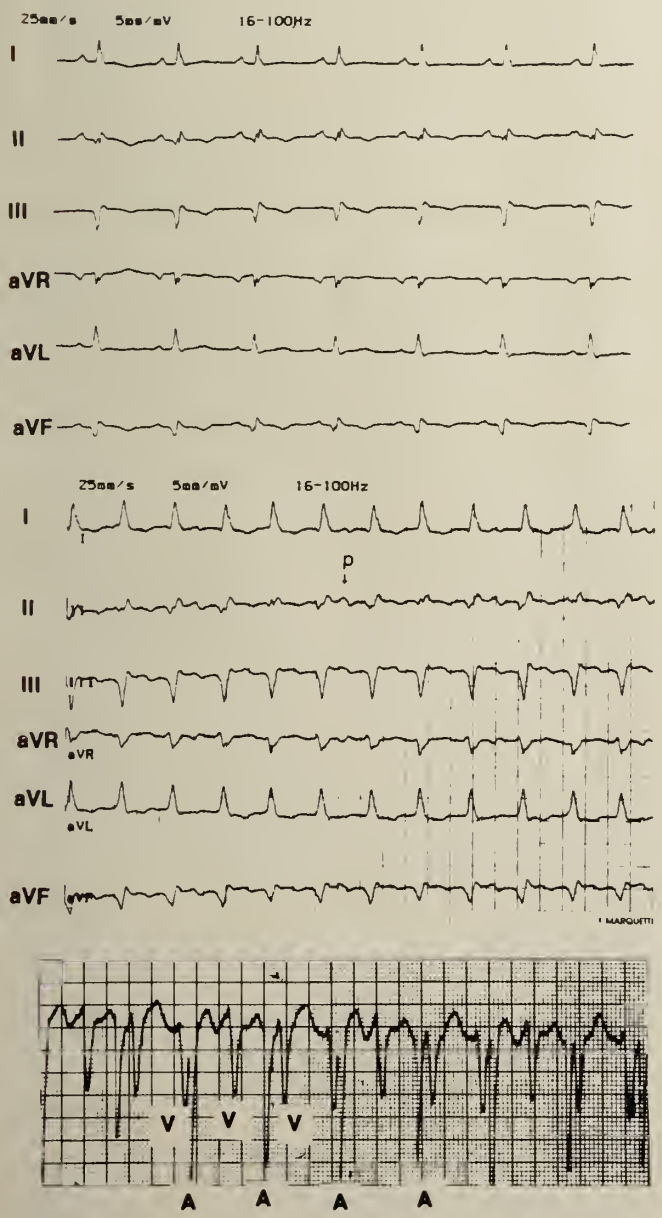



**Figure 6.**—Electrocardiograms were taken during sinus rhythm **(top)** and ventricular tachycardia **(middle)** in patient 6. During tachycardia there is a suggestion of atrioventricular dissociation **(p)**, which is confirmed by an intra-atrial electrogram **(bottom)**. A = atrial electrogram, V = ventricular electrogram

According to Kremers and co-workers, a combination of precordial QRS concordance, a monophasic R wave in $V_1$, a right superior axis, and an R wave of longer than 30 milliseconds in $V_1$ or $V_2$ strongly suggest a diagnosis of ventricular tachycardia in patients with underlying left bundle branch block.[10] Few patients with supraventricular tachycardia were studied, however, and these criteria might be of limited value in the diagnosis of such patients.

The clinical "rule" that underlying bundle branch block and similar tachycardia morphology favor the diagnosis of supraventricular tachycardia would have led to an erroneous diagnosis in the six patients in this series. In each case, there were subtle differences between the initial deflection of the QRS complex in sinus rhythm and ventricular tachycardia in some leads, suggesting that the tachycardia might not be supraventricular in origin. For example, patient 5 had a small R wave in $V_1$ during her left bundle branch tachycardia. Wellens[4] has said that this is highly suggestive of ventricular tachycardia. In four patients (3, 4, 5, and 6), the QRS duration was wider than that seen during sinus rhythm. A careful analysis of ECGs shows atrioventricular dissociation in patients 2 and 6. All patients had a history of a previous myocardial infarction with subsequent tachycardias, which in the series of Tchou and colleagues was associated with the diagnosis of ventricular tachycardia 95% of the time.[9]

In patients with underlying ventricular conduction disturbances, tachycardia of wide QRS complexes should not automatically be assumed to be supraventricular in origin even if the QRS morphology is similar to that seen on a sinus rhythm tracing. Differences in the QRS complex between sinus rhythm and the tachycardia may be subtle but can lead to the diagnosis of ventricular tachycardia. Other information should be integrated as well. The hemodynamic status should be assessed, but it is important not to let relative hemodynamic stability lead inappropriately to the diagnosis of supraventricular tachycardia.[11] Physical examination findings may occasionally be suggestive of atrioventricular dissociation. These findings include a pronounced variation in systolic blood pressure; a regular pulse with variable amplitude; variable first heart sound; and the presence of Cannon A waves on neck vein examination, which signify atrial contraction against a closed tricuspid valve. Although these findings may be useful in some patients, physicians need to be cautious in applying these criteria toward clinical decision making without further corroborative data. If other clinical clues such as those obtained from multiple surface ECG leads, esophageal leads, or vagal maneuvers do not make the diagnosis clear, then it is safer to err on the side of diagnosing ventricular tachycardia. The use of verapamil hydrochloride as a diagnostic maneuver can have disastrous hemodynamic consequences[6,12] and should therefore be avoided. If an antiarrhythmic drug is to be administered diagnostically, procainamide hydrochloride or lidocaine hydrochloride are

more appropriate choices. A response to the use of either of these drugs is not diagnostic, however, as both may be effective in the treatment of ventricular or supraventricular tachycardia. Cardioversion remains the treatment of choice for hemodynamically unstable patients. After sinus rhythm is restored, an elective electrophysiologic study can determine if the rhythm was supraventricular or ventricular in origin and can be used to guide subsequent therapy.

### REFERENCES

1. Marriott HG: Differential diagnosis of supraventricular and ventricular tachycardia. Geriatrics 1970; 25:91-101

2. Wellens H, Bart F, Lie K: The value of the electrocardiogram in the differential diagnosis of a tachycardia with a widened QRS complex. Am J Med 1978; 64:27-33

3. Akhtar M: Wide QRS tachycardia as a clinical problem. Cardiology 1988; 2:1-11

4. Wellens HJ: The wide QRS tachycardia (Editorial). Ann Intern Med 1986; 104:879

5. Dancy M, Camm AJ, Ward D: Misdiagnosis of chronic recurrent ventricular tachycardia. Lancet 1985; 2:320-323

6. Stewart R, Bardy G, Greene HL: Wide complex tachycardia: Misdiagnosis and outcome after emergent therapy. Ann Intern Med 1986; 104:766-771

7. Dongas J, Lehmann M, Mahmud R, et al: Value of preexisting bundle branch block in electrocardiographic differentiation of supraventricular from ventricular origin of wide QRS tachycardia. Am J Cardiol 1985; 55:717-721

8. Kindwall K, Brown J, Josephson M: Electrocardiographic criteria for ventricular tachycardia in wide complex left bundle branch block morphology tachycardias. Am J Cardiol 1988; 61:1279-1283

9. Tchou P, Young P, Mahmud R, et al: Useful clinical criteria for the diagnosis of ventricular tachycardia. Am J Med 1988; 84:53-56

10. Kremers MS, Black WH, Wells PJ, et al: Effect of preexisting bundle branch block on the electrocardiographic diagnosis of ventricular tachycardia. Am J Cardiol 1988; 62:1208-1212

11. Morady F, Baerman JM, DiCarlo LA Jr, et al: A prevalent misconception regarding wide-complex tachycardias. JAMA 1985; 254:2790-2792

12. Buxton A, Marchlinski F, Doherty J, et al: Hazards of intravenous verapamil for sustained ventricular tachycardia. Am J Cardiol 1987; 59:1107-1110

Clinical Medicine

# Parenteral Nutrition Use at a University Hospital

## Factors Associated With Inappropriate Use

STEVEN J. KATZ, MD, *Seattle, and* ROBERT K. OYE, MD, *Los Angeles*

*To evaluate the appropriateness of parenteral nutrition in hospital inpatients, we retrospectively reviewed the medical record of every third consecutive patient receiving parenteral nutrition admitted to a university hospital over 10 months. Of 186 patients, 71 (38%) were given this nutritional support for 7 days or fewer (short-term use). Patients who received it exclusively through peripheral catheters were more likely to receive it short term. Among 72 patients receiving it perioperatively, those who were given support for uncomplicated surgical procedures or procedures complicated by postoperative ileus were more likely to receive it short term. We conclude that a substantial amount of parenteral nutrition use results in brief durations of support for conditions that are uncomplicated or self-limited. We have identified factors associated with this inappropriate use. A prospective consideration of these data could lead to the better use of this expensive form of nutritional support.*

(Katz SJ, Oye RK: Parenteral nutrition use at a university hospital—Factors associated with inappropriate use. West J Med 1990 Jun; 152:683-686)

Parenteral nutrition has become an accepted form of nutritional support in patients admitted to hospital, and there has been a dramatic increase in its use over the past ten years. Anderson and Steinberg estimated that 550,000 patients received some form of parenteral nutrition in 1985 at a cost of more than $1 billion.[1]

Like many medical technologies, the diffusion of parenteral nutrition into clinical practice has been unpredictable. Initial studies examined its role in the perioperative setting. Subsequent studies examined its use in patients undergoing cancer chemotherapy or patients with poor oral intake due to inflammatory bowel disease, renal failure, hepatic failure, cancer, or pancreatitis.[2-12]

Recent clinical trials have raised some doubt about the efficacy of parenteral nutrition in reducing morbidity and mortality in several of these clinical settings. Detsky and coworkers did a meta-analysis of its perioperative use to ascertain whether published studies show more good than harm.[13] Pooled data from randomized controlled trials failed to show a statistically significant benefit in patients undergoing gastrointestinal surgical procedures. Because of the low number of severely malnourished patients included in the analysis, however, the results for this group were inconclusive. Detsky and colleagues then examined the use of parenteral nutrition during intensive chemotherapy (12 trials), renal failure (4 trials), inflammatory bowel disease (3 trials), and hepatic failure (9 trials). They concluded that for three of four conditions, the evidence was inconclusive and that for patients receiving chemotherapy, parenteral nutrition may be harmful.[14]

The American College of Physicians Health and Policy Committee's position paper on the perioperative use of parenteral nutrition stated that it should only be used in severely malnourished patients in hospital undergoing major gastrointestinal surgical procedures or in moderately to well-nourished patients who will not use their gastrointestinal tract for ten days or more.[15]

Koretz summarized randomized clinical trials of the use of parenteral nutrition in patients with cancer anorexia, perioperatively, and in patients with inflammatory bowel disease and concluded that no clinical trial on its use has shown a statistically significant reduction in morbidity or mortality for these indications.[16]

In contrast, the American Society for Parenteral and Enteral Nutrition published guidelines for its use in adults admitted to hospital in 1986.[17] The society recommended it be used for patients undergoing chemotherapy or a major operation or who have pancreatitis, sepsis, inflammatory bowel disease, severe diarrhea, or trauma. Parenteral nutritional support was deemed appropriate under these conditions if an enteral diet could not be resumed for seven to ten days depending on the nutritional state of the patient.

We used a conservative measure of inappropriateness derived from this literature (administration for seven days or fewer) to evaluate its use at a university hospital.

### Patients and Methods

The study took place at a 700-bed university teaching hospital. We identified the inpatient use of parenteral nutrition over a ten-month period (March 1987 to January 1988) from a log maintained by the parenteral nutrition pharmacist. All such orders were filled by the parenteral nutrition pharmacist. We retrospectively reviewed the medical records of every third patient within this sample. Parenteral nutrition was defined as an intravenous feeding regimen containing hypertonic glucose (at least 10%) and either amino acids, lipids, or both. Only patients 18 and older were included in the study group.

From the Robert Wood Johnson Clinical Scholars Program, University of Washington School of Medicine, Seattle (Dr Katz), and the Department of Medicine, University of California, Los Angeles, School of Medicine (Dr Oye).

Reprint requests to Steven J. Katz, MD, Robert Wood Johnson Clinical Scholars Program, HQ-18, University of Washington, Seattle, WA 98105.

The following data were abstracted: age, sex, attending physician, admitting service, insurance status, length of stay, discharge diagnoses, surgical procedures, indication for parenteral nutrition, type and duration of support, reason for cessation, route of administration, monitoring, duration of no oral intake (defined as the duration from the initiation of no oral intake to the restoration of a full diet), the presence of gastrointestinal symptoms or an altered mental state, albumin level, weight, height, disposition, and the presence of a consultation note on the use of parenteral nutrition. In addition, for four days of its administration per admission, we collected data on the infusion ordered and the infusion received. These days were chosen at a time when the infusion regimen was steady with no changes during the 24-hour sample period.

The average caloric intake was determined by averaging the daily dextrose and amino acid infusion over the sample days for each patient. The amount of lipids infused was averaged for a 24-hour period and added to the caloric intake.

We considered the use of parenteral nutrition to be inappropriate if the duration of administration was seven days or fewer. Patients who received this support for seven days or fewer were considered to have "short-term use" versus receiving it longer (long-term use).

Data on the average daily charges for parenteral nutrition were obtained through the medical center pharmacy and therapeutics division.

Records were abstracted by four trained abstractors: three nurse specialists in parenteral nutrition and a medical student. Differences among patient subgroups with regard to the duration of use, caloric intake, and other data were tested using $\chi^2$ and the Mann-Whitney rank sum test. A two-tailed $P$ value of .05 was considered significant.

## Results

Over a ten-month period (March 1987 to January 1988), 670 patients received parenteral nutrition during 710 admissions. We sampled 238 patients for whom the medical records of 86% (205) were available for review. The median patient age was 50 years, 100 were men and 105 women, and the median length of hospital stay was 21 days. In all, 87 patients were admitted to a medicine service and 128 to one of four surgery services—general surgery 70%; obstetrics and gynecology 12%; urology 8%; and ears, nose, and throat 2%. These patients had a variety of insurance sources: 165 patients had private insurance, 60 had Medicare, and 36 had medicaid. During admission 32 patients (16%) died, 25 while receiving parenteral nutrition. Malignant tumors were the most common discharge diagnosis (Table 1). Gastrointestinal operations accounted for 67% of the 72 patients undergoing surgical procedures.

The most common indications for initiating parenteral nutrition were perioperative support through the no-oral-intake period, cancer anorexia associated with chemotherapy, nonspecific cachexia (defined as prolonged periods of anorexia not attributable to a specific cause), and inflammatory bowel disease (Table 2).

A few patients (19) were admitted to the hospital while receiving parenteral nutrition at home or for initiating its use at home, while 186 received it only in the hospital. The rest of the analysis excludes those receiving home parenteral nutrition (n = 186).

The median duration of the administration of parenteral nutrition was 9.5 days (the range 1 to 147 days). The duration of administration was 7 days or fewer in 71 (38%). A total of 66 patients (35%) received it exclusively through a peripheral venous catheter; 30 (16%) received support exclusively through a central venous catheter, and 90 (48%) received support through a combination of the two.

The short-term use of parenteral nutrition—defined as a duration of seven days or fewer—was associated with the type of vascular access. Of 66 patients who received it exclusively by peripheral catheter, 44 (67%) received it short term (versus 23% who received it through a central or peripheral catheter, or both; $P < .001$).

There were significant variations in the duration of nutritional support and no-oral-intake period among the 72 patients receiving parenteral nutrition perioperatively. The median duration of administration was nine days. Half of the patients had no oral intake for seven days or fewer. The 41 patients receiving total parenteral nutrition for uncomplicated surgical procedures or procedures complicated only by postoperative ileus had high rates of short-term use: 56% of these patients were short-term users versus 23% for all other surgical indications ($P < .01$); 64% had no oral intake for seven days or fewer. Figure 1 shows the distribution of short-term users by surgical indication.

Among the 114 patients who received parenteral nutrition

TABLE 1.—*Most Common Discharge Diagnoses (n=205)*

| *Diagnosis* | *Patients No. (%)* |
|---|---|
| Solid tumors | 54 (26) |
| Leukemia/lymphoma | 22 (11) |
| Inflammatory bowel disease | 16 ( 8) |
| Liver disease | 16 ( 8) |
| Cardiovascular disease | 15 ( 7) |
| Sepsis | 14 ( 7) |
| Pneumonia | 13 ( 6) |
| Trauma | 11 ( 5) |
| Altered mental state | 9 ( 4) |
| Renal failure | 5 ( 2) |
| Acquired immunodeficiency syndrome | 4 ( 2) |
| Pancreatitis | 4 ( 2) |
| Other* | 22 (11) |

*Other diagnoses include (<3 patients) cardiovascular events, arthritis, chronic diarrhea, or abdominal pain.

TABLE 2.—*Most Common Indications For Initiating Parenteral Nutrition (n=205)*

| *Indication* | | *Patient, No. (%)* |
|---|---|---|
| Surgical procedures | | 72 (35) |
| No complications | 27 | |
| Complications | 45 | |
| Cancer anorexia | | 23 (11) |
| Failure to thrive | | 18 ( 9) |
| Inflammatory bowel disease | | 17 ( 8) |
| Bowel obstruction | | 14 ( 7) |
| Bone marrow transplant | | 11 ( 5) |
| Sepsis | | 9 ( 4) |
| Hepatic failure | | 7 ( 3) |
| Chronic diarrhea | | 6 ( 3) |
| Other* | | 28 (14) |

*Other indications include (<3) short bowel syndrome, radiation enteritis, renal failure, pancreatitis.

for nonsurgical indications, the pattern of use was more diffuse. The median duration of its administration was eight days. A total of 60 patients (51%) received no oral intake during some portion of the administration period. Patients receiving support for nonspecific cachexia (defined as poor oral intake without a specific cause), hepatic failure, and chronic diarrhea had higher rates of short-term use than those for all other indications (59% versus 26%, respectively; $P<.05$). Table 3 breaks down the duration of administration by indication.

There was a wide distribution of attending physicians (76), diagnoses (29), and indications for therapy (19) among all users. Of the 76 attending physicians who ordered parenteral nutrition, 50 were subspecialists and 26 were general internists or general surgeons. Four physicians accounted for 26% of the ordering and 45 ordered support only once. There was no significant difference in the number of patients receiving nutritional support for seven days or fewer between physicians treating ten or more patients (n=4) and physicians treating fewer than five patients (n=72), 38% versus 40%, respectively (not significant).

Albumin level and body-mass index were used to assess the nutritional state at the time of the initiation of parenteral nutrition. The median albumin level was 31 grams per liter (normal 35 to 50), and the median body-mass index was 22.5 kg per $m^2$ (normal 22 to 25). The albumin level and body-mass index did not vary significantly by the duration of parenteral nutrition, indication, route of administration, or admitting service.

To determine the number of calories ordered and received in a 24-hour period, we collected data on a sample of 855 days of parenteral nutrition administration (approximately 4 days per admission). The mean number of calories ordered and received was 2,018 and 1,719, respectively. The total number of calories infused in a 24-hour period was 90% or more of the order in 598 (70%) of the days sampled. About 11% of patients received 70% or less of the calories ordered. Conflicts with the administration of blood transfusions and antibiotics were the cause in most of these cases.

The number of daily calories delivered varied widely with the route and duration of administration. Patients receiving support by peripheral access received fewer calories (1,370 versus 1,972 by central access, $P<.01$). Short-term users received fewer calories (1,559) than did long-term users (1,840; $P<.01$). Among 186 patients, 39 received only carbohydrate and protein without lipid infusion.

The daily charge for parenteral nutrition averaged $240 over the study period (1987 dollars). The total charge per admission varied as a function of the duration of support and complexity of the solution. The bone marrow transplant unit averaged $6,772 of parenteral nutrition charges per admission while the gynecology service averaged $2,380.

## Discussion

In the institution studied, parenteral nutrition was used by all medical and surgical services in a wide range of clinical settings. It has grown from a form of specialized nutritional support with relatively narrow indications to one adopted by specialists and nonspecialists for a large number of clinical indications.

Our study identified a large number of patients (38%) who received parenteral nutrition for short durations (7 days or fewer) in uncomplicated surgical or medical settings. These patients received fewer daily calories largely by peripheral catheter access. Many of these patients had relatively brief, self-limited periods of decreased oral intake. For example, patients who received parenteral nutrition perioperatively for uncomplicated procedures or procedures complicated by postoperative ileus had no oral intake for an average of six days. Although the appropriate indications for parenteral nutrition and the duration of support are controversial among physicians, a consensus has emerged in the direction of more conservative use. For instance, the American College of Physicians recommends its perioperative use in malnourished patients undergoing major gastrointestinal surgical procedures only when the period of no oral intake is expected to be ten days or more.[15] Parenteral nutrition given

TABLE 3.—*Duration of Parenteral Nutritional Support By Indication (n=186)**

| Indication | Patients, No. 7 Days or Fewer | 8 to 10 Days | 10 Days or More |
|---|---|---|---|
| *Perioperative Indications* | | | |
| No complications | 15 | 5 | 7 |
| Ileus | 8 | 4 | 2 |
| Other complications† | 7 | 6 | 18 |
| *Nonoperative Indications* | | | |
| Nonspecific cachexia | 10 | 3 | 6 |
| Hepatic failure | 4 | 1 | 2 |
| Chronic diarrhea | 5 | 1 | 0 |
| Sepsis | 3 | 2 | 3 |
| Inflammatory bowel disease | 2 | 1 | 7 |
| Cancer chemotherapy | 6 | 3 | 14 |
| Bone marrow transplant | 0 | 1 | 10 |
| Bowel obstruction | 2 | 4 | 5 |
| Trauma | 1 | 0 | 9 |
| Other | 2 | 0 | 7 |

*Excludes patients admitted for initiation of home parenteral nutrition.
†Infectious, cardiovascular, or operative complication.

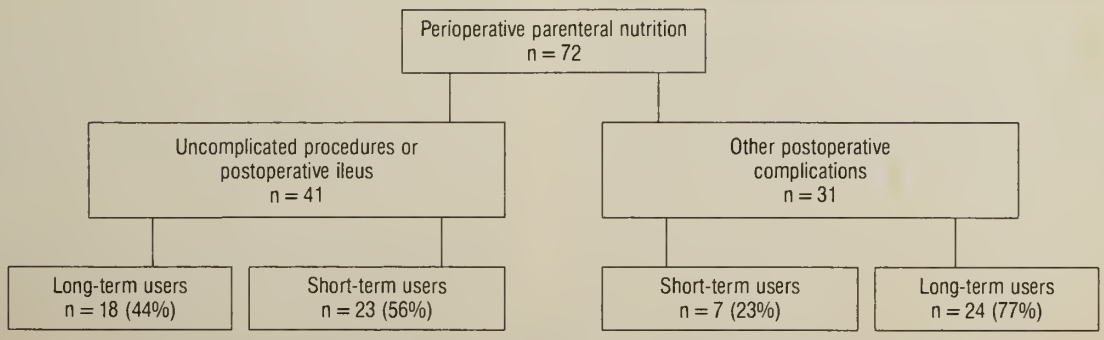



**Figure 1.**—The diagram shows the duration of perioperative nutritional support.

for short durations during brief periods of decreased oral intake is unlikely to be beneficial. We think that our cutoff of infusion for seven days or fewer is a conservative estimate of inappropriate use.

By identifying the factors that are associated with short-term use, inappropriate use can be prospectively recognized. We have detected such factors at our institution. Among surgical patients, uncomplicated surgical procedures or procedures complicated by self-limited conditions such as ileus were strongly associated with short-term use. Many of the medical patients who received parenteral nutrition for short durations had obscure indications for support, such as nonspecific cachexia or chronic diarrhea, and were likely to have no specific nutritional intervention plan. Finally, parenteral nutrition delivered exclusively through a peripheral catheter resulted in a high rate of short-term use.

Short-term use was spread among a large number of physicians. Of the 76 attending physicians who ordered parenteral nutrition during the study period, 4 treated ten or more patients; the other 72 averaged fewer than two. These four physicians treating more patients had a similar rate of short-term use as the 72 who treated fewer. Although all orders were written by interns and residents, it was our impression that the decision to initiate nutritional support was made with substantial input at the attending level.

We think there are several reasons why parenteral nutrition is overused at the institution studied. It appears that it is being considered one of the many choices of intravenous hydration without a consideration of the expense. Physicians may not be appraised of the current controversy over its efficacy. The relative ease of ordering and administration also contributes to overuse, especially among patients receiving support exclusively through a peripheral catheter. In addition, physicians appear to focus on the nutritional state of a patient rather than on the self-limiting nature of the decreased oral intake period under certain conditions. Although in our study, the nutritional state as measured by albumin levels and body-mass index indicated that, as a whole, patients placed on a regimen of parenteral nutrition were moderately malnourished, this index did not vary by the duration of the decreased oral intake period, duration of use, indication, diagnosis, service, or route of administration.

The cost of monitoring parenteral nutrition use is likely to be offset by any diminution in its use. Parenteral nutrition is expensive. At our institution, the daily pharmacy charges averaged $240. These charges must be interpreted carefully because they are only proxies for hospital costs. They include profits but exclude the cost of laboratory tests, intravenous catheters, infusion pumps, complications, or nursing time.[18]

There are several factors that potentially limit the conclusions of this study. The cessation of therapy because of death could spuriously increase the number of patients designated as short-term users. In a secondary analysis, we excluded all 25 patients who died during the administration of parenteral nutrition, 10 of whom received support for seven days or fewer. There were no changes in statistically significant results.

Some patients may have received short-term nutritional support even though they were without substantial oral intake for longer periods. In these patients support could have begun several days after the period of decreased oral intake began. Of the 71 patients who received parenteral nutrition for seven days or fewer, only 6 had no oral intake for ten days or longer (range 11 days to 21 days). In four cases enteral support was begun; in one case, the use of parenteral nutrition was terminated early because of fluid overload and renal failure. In only one case was the infusion regimen begun late in the course of the no-oral-intake period.

The study was restricted to one university teaching hospital, and, therefore, the results should not be generalized to other settings.

In summary, parenteral nutrition was used widely by all services of the hospital for diverse indications. We have identified a large number of cases of the use of parenteral nutrition for brief periods in which it was unlikely to be beneficial. We have identified factors associated with its short-term use. A prospective consideration of these factors may improve the use of this expensive and potentially morbid form of nutritional support.

## REFERENCES


1. Anderson GF, Steinberg EP: DRGs and specialized nutrition support—Prospective payment and nutritional support: The need for reform. JPEN J Parenter Enteral Nutr 1986; 10:3-8

2. Szeluga DJ, Stuart RK, Brookmeyer R, et al: Nutritional support of bone marrow transplant recipients: A prospective, randomized clinical trial comparing total parenteral nutrition to an enteral feeding program. Cancer Res 1987; 47:3309-3316

3. Popp MB, Fisher RI, Wesley R, et al: A prospective randomized study of adjuvant parenteral nutrition in the treatment of advanced diffuse lymphoma: Influence on survival. Surgery 1981; 90:195-203

4. Samuels ML, Selig DE, Ogden S, et al: IV hyperalimentation and chemotherapy for stage III testicular cancer: A randomized study. Cancer Treat Rep 1981; 65:615-627

5. Nixon DW, Mottiff S, Lawson DH, et al: Total parenteral nutrition as an adjunct to chemotherapy of metastatic colorectal cancer. Cancer Treat Rep 1981; 65 (Suppl 5):121-128

6. Dickinson RJ, Ashton MG, Axon ATR, et al: Controlled trial of intravenous hyperalimentation and total bowel rest as an adjunct to the routine therapy of acute colitis. Gastroenterology 1980; 79:1199-1204

7. Greenberg GR, Fleming CR, Jeejeebhoy KN, et al: Controlled trial of bowel rest and nutritional support in the management of Crohn's disease. Gastroenterology 1985; 88:1405-1409

8. Abel RM, Beck CH, Abbott WM, et al: Improved survival from acute renal failure after treatment with intravenous essential L-amino acids and glucose. N Engl J Med 1973; 288:695-699

9. Leonard CD, Luke RG, Siegel RR: Parenteral essential amino acids in acute renal failure. Urology 1975; 6:154-157

10. Cerra FB, Cheung NK, Fischer JE, et al: A multicenter trial of branched chain enriched amino acid infusion in hepatic encephalopathy. Hepatology 1982; 2:699-705

11. Gluud C, Dejgaard A, Hardt F, et al: Copenhagen Coma Group—Preliminary treatment results with balanced amino acid infusions patients with hepatic encephalopathy. Scand J Gastroenterol 1983; 18 (Suppl 86):19-22

12. Sax HC, Warner BW, Talamini MD, et al: Early total parenteral nutrition in acute pancreatitis: Lack of beneficial effects. Am J Surg 1987; 153:117-124

13. Detsky AS, Baker JP, O'Rourke K, et al: Perioperative parenteral nutrition: A meta-analysis. Ann Intern Med 1987; 107:195-203

14. Detsky AS, Baker JP, McGeer A, et al: Is parenteral nutrition an effective supportive therapy? The evidence from randomized trials (Abstr). Clin Res 1989; 37:310A

15. American College of Physicians Health and Policy Committee: Position paper: Perioperative parenteral nutrition. Ann Intern Med 1987; 107:252-253

16. Koretz RL: Nutritional support: How much for how much? Gut 1986; 27 (Suppl):85-95

17. ASPEN Board of Directors: Guidelines for use of total parenteral nutrition in hospitalized adult patients. JPEN J Parenter Enteral Nutr 1986; 10:441-445

18. Eisenberg JM, Glick H, Hillman AL, et al: Measuring the economic impact of perioperative total parenteral nutrition: Principles and design. Am J Clin Nutr 1988; 47 (Suppl):382-391

Medical Progress

# Current Status of Renal Transplantation

MICHAEL G. SURANYI, MBBS, FRACP, *and* BRUCE M. HALL, MBBS, FRACP, PhD, *Stanford, California*

*The success rate of renal transplantation has improved considerably during the past decade, with substantial improvements in both graft and patient survival. The quality of graft function, however, and not graft survival alone is increasingly determining the standards by which transplantation outcome is being judged. As the demand for kidney transplants continues to rise and transplants are being offered to an ever-increasing number of patients, organs are being sought from new supply pools and efforts are being made to use current resources more efficiently. Improvements in clinical management have allowed short-term complications such as infection and rejection to be better prevented or better diagnosed and treated. Fundamental advances in the understanding of the immunologic processes underlying both allograft rejection and acceptance and the introduction of new immunosuppressive agents have allowed a better use of drug therapy and have moved the goal of acquired transplant tolerance closer to attainment. With improved initial transplant success rates, the long-term transplantation outcome is becoming more important. The role of tissue matching in preventing chronic rejection is becoming more appreciated, and the long-term risks of malignancy, arteriosclerosis, and chronic rejection are being better recognized and managed.*

(Suranyi MG, Hall BM: Current status of renal transplantation. West J Med 1990 Jun; 152:687-696)

In the 1980s the success rate of cadaver-donor renal transplantation improved from one-year graft survival rates of around 50% to rates of 75% to 85%. At the same time, patient survival rates also improved, with one-year patient survival generally greater than 95%.[1-3] During the past decade, there have been parallel improvements in the detailed understanding of the fundamental processes causing rejection.[4,5] In clinical transplantation, improvements have been made in tissue typing, immunosuppression, and patient care and in the management of rejection, the diagnosis and treatment of acute and chronic allograft dysfunction, and the diagnosis and treatment of immunosuppression-related problems such as malignancy and infection.

Despite the continued relative shortage of cadaveric donor kidneys, renal transplantation grafting rates are progressively rising. The number of kidney transplants is increasing as groups of patients previously denied them—including those sensitized to HLA antigens,[6] the elderly,[7-9] the very young,[10] and high-risk patients[11]—receive kidneys.

The solution to the shortage of kidneys lies first with the optimal use of currently available cadaver kidneys and, second, in harvesting grafts from new patient pools, such as kidneys from pediatric and elderly donors[12-14] and from living-related and unrelated donors.[15-17]

## Pretransplantation Measures to Improve Graft Survival

### *Tissue Typing*

The most important transplantation antigens in humans and animal models are determined by a polymorphic group of genes, the major histocompatibility complex (MHC), which in humans are called human leukocyte antigens. The protein products of these genes are present on most cell surfaces and fall into two important classes: the HLA class I antigens (including HLA-A, -B, and -C) and the HLA class II antigens (including the HLA-DR, -DP, -DQ, and other D-related antigens). A set, or haplotype, of these antigens is inherited from each parent and is codominantly expressed. The resolution of the x-ray crystallographic structure of HLA-A2 has shown that the normal function of HLA molecules is to present antigen, in the form of a short peptide (5 to 22 amino acids), in the groove formed on the external surface of the molecules.[18] T-cell receptors recognize only antigen presented by this complex of MHC and antigenic peptide, and specialized antigen-presenting cells provide activation signals to T cells. This antigen presentation system is designed to trigger the immune system against viral and other intracellular pathogens and tumors. In transplantation, a situation unforeseen by nature, these same mechanisms result in the activation of effector cells such as T and B cells against the foreign MHC on the cells of the allograft, and the end result is rejection.

The stimulus activating the responding immune system to induce rejection, the major cause of allograft loss, depends on the number and type of HLA mismatches between recipient and donor. The most important HLA antigen mismatches driving the rejection response have been found to be the HLA-DR and HLA-B antigens, which are also the most polymorphic.[19] The benefits of HLA matching are best manifested in grafts between relatives, where matching between donor and recipient influences both short-term and long-term allograft survival.[16]

From the Department of Medicine, Division of Nephrology, Stanford University Medical Center, Stanford, California.
Reprint requests to Bruce M. Hall, MD, Division of Nephrology, Department of Medicine, Rm S-215, Stanford University Medical Center, Stanford, CA 94305-5114.

ABBREVIATIONS USED IN TEXT

ALG = antilymphocyte globulin
CMV = cytomegalovirus
HIV = human immunodeficiency virus
IL-2 = interleukin 2
MHC = major histocompatibility complex

With the use of potent immunosuppressive protocols, early graft losses due to rejection can be suppressed, allowing the successful short-term function of even completely mismatched kidneys.[17,20] With longer follow-up, however, HLA disparity may contribute substantially to the loss of grafts with chronic rejection despite immunosuppression.[21,22] The rejection of poorly matched grafts results in a high incidence of sensitization, which can jeopardize the chances and success of subsequent transplantation and can result in a high mortality rate among patients returning to dialysis.[23] The success of second transplants may depend even more on HLA matching than does that of primary grafts.[24]

The need to establish the optimal use of a limited donor resource has led to a promotion of kidney sharing on a regional basis, with the aim of increasing the number of patients receiving well-matched grafts.[25-27] The national United Network of Organ Sharing program was set up with that aim. By current estimates an effective organ-sharing scheme could result in as many as 20% of patients being allocated A-, B-, and DR-compatible kidneys and in the number of patients receiving poorly matched kidneys being substantially reduced.[28] Organ-sharing programs may also have the benefit of reducing the number of highly sensitized patients awaiting second transplants. Nevertheless, kidney sharing is a contentious issue.[29,30] Some groups maintain that matching confers no benefit in cadaver or even living-related transplants[20] and that the longer storage required for exchanged kidneys causes damage that counterbalances any advantages of tissue-matched exchanged kidneys.[31] There has been progressive improvement, however, in the cold storage preservation of cadaveric kidneys, particularly with the introduction of the University of Wisconsin solution.[32-35] Still, it may require the application of exchange incentives to improve cooperation to produce an effective allograft exchange program.[36]

*Lymphocytotoxic Antibody Crossmatch*

After excluding ABO blood group incompatibility, testing for lymphocytotoxic antibodies against HLA class I and class II constitutes one of the most important matching procedures before transplantation. Such antibodies arise as a consequence of blood transfusion, pregnancy, and a previous transplant rejection.[37] The presence of antibody reacting with donor lymphocytes is excluded before transplantation, as such antibody has been associated with hyperacute and accelerated rejection.[38] Transplantation generally does not take place if deleterious lymphocytotoxic antibodies are detected in the crossmatch test before the procedure.[39]

Numerous controversies remain unresolved regarding the techniques and criteria of such testing,[40] including the relative value of historic and current antidonor crossmatches, the merits of anti-T- and anti-B-cell crossmatches,[41] the relative importance of sensitive assays such as fluorescence-activated cell sorting,[42-44] and the use of antiglobulin reagent in the cytotoxic crossmatch.[45] The crossmatch test does not identify antibodies against organ-specific antigens that are not expressed on donor lymphocytes.[46] Such antibodies may be found in the serum or allograft of a recipient[47] and may also play an important role in rejection processes.[48]

An increasing number of patients awaiting transplantation show a high degree of sensitization, which makes it difficult to find a compatible donor. This trend is exacerbated by the number of patients awaiting second transplants after the rejection of poorly matched first grafts. Many efforts to reduce the incidence of such presensitization have been ineffective,[49] but grafts bearing maternal HLA antigens may be useful in such sensitized recipients.[50] Highly sensitized patients do best when receiving transplants using well-matched grafts,[24] but such patients have also had successful transplants without regard to HLA matching.[51] Attempts have been made to reverse the sensitized state by plasmapheresis, antibody adsorption, and cyclophosphamide therapy, but these are still experimental.[52,53] Similar protocols have been used to remove hemagglutinins in recipients of ABO-incompatible grafts.

*Blood Transfusion*

In 1973 Opelz and co-workers noted a beneficial effect of random blood transfusion on the outcome of transplantation,[54] and this was subsequently confirmed by many groups. The recognition of the therapeutic benefits of random transfusion was followed shortly by the introduction of donor-specific blood transfusions in a subset of living-related transplant recipients.[55] Both random and donor-specific blood transfusions have been associated with a significant incidence of sensitization,[56] which can preclude subsequent transplantation. It has been postulated that donor-specific transfusion results in directly sensitizing recipients, whose reactive immune cells are then depleted by heavy immunosuppression soon after the transplantation.[57]

The role of blood transfusion as an adjunct to transplantation is now in question,[58] and the risk of sensitization and of the transmission of viral and other pathogens—particularly the human immunodeficiency virus (HIV)—must be weighed against the potential benefits. Further, with the introduction of recombinant erythropoietin,[59] the need to transfuse dialysis patients for anemia will be largely eliminated. If transfusion is required, however, using HLA-matched transfusions may reduce sensitization.[60] Recent data in the International Collaborative Transplant Study have led Opelz to suggest that there is now no compelling reason to undertake either random or donor-specific transfusion.[61]

## Immunosuppressive Protocols

Immunosuppressive agents commonly used include azathioprine, prednisone, cyclosporine, antilymphocyte globulin (ALG) preparations, anti-CD3 monoclonal antibody (Orthoclone OKT3), ionizing irradiation,[62] and alkylating agents such as cyclophosphamide.[63] Azathioprine and prednisone were the mainstay of therapy in the 1960s and 1970s, and antilymphocyte globulin was added in the late 1960s. Cyclosporine became available in the 1980s and is now central to most protocols.

The introduction of cyclosporine has been associated with a period of progressive improvement in the success of renal transplantation,[64] which has also been translated into an improvement in quality of life for patients.[65,66] The mechanisms

of its actions are still being investigated, but it effectively inhibits the release of cytokines, especially interleukin 2 (IL-2), known to be important in the generation of the rejection response.[67-69] The main side effect of cyclosporine is, paradoxically, nephrotoxicity.

Cyclosporine was initially used alone or with prednisone, but to minimize side effects, particularly nephrotoxicity that occurs at high dosage, there has been a trend toward combining agents at a lower dosage to achieve additive or synergistic effects.[70] The rationale of multiple-agent protocols is that each immunosuppressive acts at different sites in the immune system. By using lower doses of each agent, it is hoped that the side effects of higher doses will be avoided while the benefits of each agent are retained. Triple-drug therapy with azathioprine, prednisone, and cyclosporine has become widely used, as has quadruple-drug therapy, with ALG induction followed by triple-drug therapy.[70] Despite the general tendency to use multiple agents, some transplant centers continue to use one- or two-drug protocols with comparable graft survival rates.[71,72] The combination of cyclosporine and azathioprine as maintenance therapy can avoid the long-term use of steroids.[73,74]

The main factor driving the trend toward multiple-drug therapy is the nephrotoxicity of cyclosporine, the use of which can increase the duration of early nonfunction of a transplanted kidney.[75] To minimize early nonfunction, some protocols include low doses of cyclosporine whereas others avoid the early use of cyclosporine by using ALG, azathioprine, and prednisone followed by cyclosporine only after adequate renal function occurs.[70]

Combination immunosuppression still does not completely prevent rejection episodes or graft loss, especially in second transplants or in patients who do not have good tissue matching.[3,76] Combined therapy may also be associated with a substantial risk of patient morbidity from opportunistic infection[77] or a malignant lesion such as lymphoma.[78] For this reason prophylactic broad-spectrum antibiotics and acyclovir may be used to prevent infection.[79] Monitoring cyclosporine levels in whole blood, serum, or plasma to adjust the dosage is widely done to minimize the side effects of using cyclosporine.[80-83] Because of nephrotoxicity, cost, and the unknown effects of long-term cyclosporine use, some centers have begun converting from cyclosporine to conventional azathioprine and prednisone therapy.[84] The main reason for converting from initial cyclosporine therapy is the relatively high incidence of cyclosporine nephrotoxicity and its progressive and ultimately irreversible nature.[85] The conversion from cyclosporine use can result in improved renal function and blood pressure control,[71,86,87] and these benefits appear to persist.[87] There can be a major risk of acute rejection and loss of the graft if conversion is undertaken before rejection is carefully excluded, however.[70,88,89] Patients undergoing conversion for refractory rejection have a high risk of graft loss.

Although cyclosporine therapy is undoubtedly effective against cell-mediated acute rejection, its effect on chronic rejection is less certain,[90] and distinguishing chronic rejection from nephrotoxicity may be difficult.

*Monoclonal Antibodies*

Monoclonal antibody therapy, the most successful example of which is OKT3, became available shortly after cyclosporine was introduced. Polyclonal antilymphocyte antibody preparations (ALG) have had a place in renal transplantation for many years and continue to contribute to immunosuppression protocols.[91] Preparations of ALG, however, have suffered from variation between batches and from side effects associated with their many specificities.[70] Now monoclonal antibodies are being developed that have greater purity, specificity, and reproducible biologic activity. Their use has provided a mechanism for precisely targeting antibody-mediated effects to one cell surface molecule. In renal transplantation this allows immunosuppressive therapy that is more specific than using agents such as azathioprine, steroids, and cyclosporine. On the T-cell surface many antigens provide a target for such specific therapy.[92] Of these, an antibody against CD3 is already in general use, and monoclonal antibodies against the IL-2 receptor and against the T12 molecule have been tested.[93] The potential usefulness of the anti-CD4 antibody has not been overlooked,[94] and efforts are being directed to develop many other monoclonal antibodies for clinical use, including those against activation antigens on T cells.[95] In addition, monoclonal antibodies against cytokines, such as interleukin 2 and interferon gamma, also require assessment as immunosuppressives in renal transplantation.[96] Investigation is also underway into the use of monoclonal antibodies, such as those to passenger leukocytes, to reduce the immunogenicity of grafts.[97]

*OKT3 Monoclonal Antibody Therapy*

OKT3, a murine monoclonal antibody of the immunoglobulin G2a class, has proved to be a potent immunosuppressive agent owing to its ability to bind the T-cell antigen-receptor complex.[98] The use of OKT3 has been effective as prophylactic therapy in renal transplantation[99,100] and as antirejection therapy,[101-105] but its most appropriate use may be as rescue therapy for steroid-resistant rejection.[106-108] OKT3 therapy has also been shown to benefit patients with predominantly vascular pattern rejection.[109] The recurrence rate of rejection, however, may be unexpectedly high after OKT3 use, as it probably does not eliminate allograft-responding T cells. Its use is thought to result initially in the opsonization and rapid removal of T cells from the circulation. Thereafter, OKT3 appears to rapidly modulate or remove the CD3 or T cell-receptor complex from the surface of T cells, rendering them incapable of activation by antigen recognition.

A number of major problems have emerged with the use of OKT3. A severe febrile reaction and bronchospastic response can follow the administration of the first dose. Pulmonary edema also occurs in patients with fluid overload.[110] The cause of systemic symptoms may be related to the demonstrated ability of OKT3 to activate T cells. This initial T-cell activation, or, alternatively, a wave of T-cell destruction, can result in the release of potent T-cell cytokines leading to systemic effects, including a fall in the glomerular filtration rate.[98,111] Cytokine increases have also been noted with ALG use.[112] After OKT3 use, particularly if high-dose immunosuppressive agents have also been used, a higher incidence of infection may be seen.[107,113,114] Finally, under certain circumstances, T cells with modulated CD3 or T cell-receptor complex may still mediate acute rejection, despite therapeutic levels of OKT3.[115]

An antibody response to OKT3 develops in most treated patients, despite concomitant immunosuppression with cyclosporine or azathioprine. These antibodies may be to the idiotype, isotype, or common determinants of mouse immunoglobulin.[98] Such antibodies may develop during an ini-

tial course, limiting its usefulness and allowing rejection to break through, but they more often develop afterwards, interfering with the use of a second course.[116,117] Reuse can be successful if high-titer anti-OKT3 antibodies have not developed,[118,119] although such reuse is associated with a high incidence of viral infection.[120]

Because anti-idiotypic antibodies developing after OKT3 therapy do not cross-react with all anti-CD3 monoclonal antibodies, using different anti-CD3 monoclonal antibodies may be one approach to reuse.[121] Further, with the use of molecular biologic techniques, human or mouse-human hybrid antibodies can be made that may not stimulate anti-mouse antibody formation.[92] It has been recently suggested that a concurrent infusion of anti-CD4 monoclonal antibody may reduce the formation of recipient anti-OKT3 antibodies by impairing helper T-cell function required for antibody formation.[122]

*Anti-Interleukin 2-Receptor Therapy*

Interleukin 2 is a critical cytokine involved with the activation, proliferative expansion, and amplification of T cell-mediated rejection responses, such as those occurring with allograft rejection.[123] The IL-2 receptor is expressed mainly on activated T cells, having a low- and high-affinity form, the latter of which binds and internalizes IL-2. In patients undergoing transplantation, the blockade or elimination of T cells expressing the IL-2 receptor can be expected to immunosuppress, in a relatively selective way, the clones responding to an allograft and mediating rejection.[124] The use of anti-IL-2 receptor monoclonal antibodies has proved effective in animal models[125] and has undergone initial trials in humans,[126,127] but not always successfully.[128] This therapy may be synergistic with cyclosporine therapy and is reported to spare suppressor cells.[129]

The initial promise of monoclonal antibody therapy using anti-IL-2 receptors has been enlarged on by the development of a novel IL-2-diphtheria toxin hybrid, which binds to the high-affinity IL-2 receptor on activated cells, mainly T cells, is internalized, and results in cell destruction.[130-132]

*Newer Agents*

The promise of less nephrotoxic analogues of cyclosporine has not yet been realized.[133] With immunosuppressive characteristics similar to cyclosporine, FK 506 has recently come to increased public attention. Similar to cyclosporine in its ability to inhibit cytokine production,[134-136] FK 506 is currently under investigation for use as a clinical renal transplant immunosuppressive agent, but it has shown considerable hepatotoxicity.[137] Investigation is also proceeding into methods of treating allografts before implantation with agents designed to reduce the ability of grafts to stimulate an immune response.[138,139]

*Efforts to Induce Transplant Tolerance*

The development of tolerance, or specific unresponsiveness, to donor tissue is the most attractive form of immunosuppression, avoiding drug complications such as infection and malignancy. Anecdotes relate long-term survival of some allografts without the benefit of continued immunosuppressive therapy for prolonged periods.[140] With the establishment of tolerance, immunosuppressive drugs would not be required, and the immune system's natural regulatory mechanism would ensure allograft survival. This ideal is still far from reality in clinical transplantation, although our increased understanding of the mechanisms of such states in animals brings it closer.[141]

In experiments in animals, total lymphoid irradiation and donor bone marrow infusion have been shown to promote a tolerant state, and the role of these agents is being investigated in humans.[142,143] Recent reviews of total lymphoid irradiation in a clinical transplant population found some patients with unresponsiveness to the donor in in vitro immune responses, suggesting that a state of specific donor unresponsiveness may develop in some patients.[144,145] Total lymphoid irradiation is effective immunosuppression, but long-term follow-up shows that patients receiving this therapy have three-year patient and graft survivals, which appear lower than the results of comparable trials using cyclosporine and prednisone.[146]

## Clinical Problems in Renal Transplantation

*The Diagnosis of Rejection*

The diagnosis and treatment of renal dysfunction early in the posttransplant period are difficult but important, because acute tubular necrosis, cyclosporine nephrotoxicity, and acute rejection are hard to distinguish clinically.[147] Percutaneous renal biopsy remains the gold standard for diagnosing the cause of renal transplant impairment, especially with the addition of monoclonal antibody markers to identify infiltrating cells and allograft antigens.[148-151] In particular, the assessment of HLA-DR expression on renal tubular cells may assist in the determination of acute rejection.[152]

Fine-needle aspiration biopsy has become a clinically useful and safe technique for sequentially monitoring graft parenchymal cells and infiltrates.[153] The application of flow cytometric and immunofluorescence technology has added increased usefulness to the technique[154,155]; although the correlation with renal allograft histologic features is good, the information provided about graft structures is more limited.

Renal ultrasonography, radionuclide studies, and magnetic resonance imaging (MRI) may all contribute to the diagnosis of renal transplant dysfunction. Nevertheless, despite their technologic sophistication, none of these methods are sufficient to distinguish among rejection, acute tubular necrosis, and cyclosporine nephrotoxicity. Rejection causes a loss of the corticomedullary demarcation on MRI, but this is not specific.[156-158] Whether MRI is more sensitive than radionuclide studies and sonography has been disputed.[159-161]

Techniques requiring further assessment include duplex Doppler sonography, which may aid in differentiating acute rejection from acute tubular necrosis or cyclosporine nephrotoxicity.[162-164]

*Cyclosporine Nephrotoxicity*

Cyclosporine nephrotoxicity remains a major problem in renal transplantation, and efforts to resolve whether the immunosuppressive effect of cyclosporine can be separated from its nephrotoxic effect have so far failed.[165] The therapeutic window is so narrow that cyclosporine nephrotoxicity and allograft rejection may coexist. Cyclosporine dosage and cyclosporine serum concentrations may not provide accurate predictors of nephrotoxicity[166-168]; nevertheless, many groups advocate protocols using lower cyclosporine dosages to lessen renal impairment.[169,170]

Cyclosporine can induce nephrotoxicity in both native

and transplanted kidneys,[171] but nephrotoxicity may be worse in kidneys that have had an ischemic insult.[172] Patients receiving cyclosporine have a higher incidence and longer duration of initial graft nonfunction,[71,173] which may result in long-term effects on graft survival.[174] For this reason some centers prefer to use sequential therapy, treating initially with other immunosuppressive agents and introducing a regimen of cyclosporine after graft function has been established.[175] Further, patients with functioning grafts who are receiving long-term cyclosporine therapy generally have a lower glomerular filtration rate than do patients receiving azathioprine and prednisone therapy.[71]

The exact mechanisms of cyclosporine nephrotoxicity are still not known but are under intensive investigation. Cyclosporine causes vasoconstriction of vascular smooth muscle,[176] with an alteration in renal hemodynamics,[177] whereas tubular function is relatively spared.[178] In addition, cyclosporine may be responsible for the arteriolopathy found in some allografts.[179] Cyclosporine may alter the thromboxane-prostacyclin balance, allowing thromboxane-induced vasoconstrictor predominance.[180-183] Certainly cyclosporine use appears to increase thromboxane $A_2$ levels,[184] and administering thromboxane inhibitors modifies the renal effects of cyclosporine.[185,186] Because cyclosporine is metabolized in the liver through the cytochrome P-450 system, drug interactions may be important in inducing elevated cyclosporine levels predisposing to nephrotoxicity. The use of erythromycin, ketaconazole, steroids, sex hormones, and some calcium channel blockers may induce elevated cyclosporine levels, and rifampin and anticonvulsant therapy may decrease cyclosporine concentrations.[187]

The use of calcium channel blockers may modify cyclosporine nephrotoxicity[188] because cyclosporine binds certain intracellular calcium-binding proteins.[189] Although it is clear that cyclosporine therapy results in lower kidney transplant function than does azathioprine and prednisone therapy,[71] its role in progressive renal impairment is in question.[190] It is best documented that long-term cyclosporine administration may be associated with progressive renal impairment in patients receiving organs other than kidneys,[191,192] where renal transplant rejection does not confuse the issue. In the long term, cyclosporine use is associated with a progressive increase in interstitial fibrosis and tubular and vascular changes.[193] Even when creatinine levels are stable, histologic damage can be detected in the allograft, and stable creatinine levels may be at the cost of increased function in hypertrophied remnant glomeruli.[85,191,194] Thus, the use of serum creatinine levels or even creatinine clearance as an indicator of kidney transplant function may not be sensitive to progressing nephrotoxicity.[195]

*Transplant-Associated Hypertension*

Hypertension has been a recurrent and persistent problem in renal transplantation.[196] The incidence of posttransplantation hypertension has increased since the widespread use of cyclosporine.[197,198] In association with the impaired lipid profile related to cyclosporine use (reviewed by Chapman and Morris),[84] hypertension may contribute substantially to the death of transplant recipients through the development of arteriovascular and cardiovascular disease.[199,200] Hypertension may also pose a threat to allograft survival.[23,201] The basis of the high incidence of hypertension in renal transplant patients includes factors such as chronic rejection, transplant renal artery stenosis, recurrent renal disease, and increased native-kidney renin production.[202,203] Cyclosporine is a potent inducer of hypertension, in a somewhat different manner from other immunosuppressive agents.[198,204,205] Cyclosporine causes subtle renal impairment,[206] even at normal therapeutic levels,[207] and its use has been associated with sodium retention.[208] The addition of prednisone therapy can also exacerbate hypertension, in part by limiting renal sodium excretion.[209]

*Opportunistic Infection*

Viral infections have the greatest potential for causing serious infectious complications in kidney transplant recipients. There is also increasing recognition of the role of viruses in triggering posttransplant malignancy, such as lymphoma, hepatoma, Kaposi's sarcoma, and genitourinary cancers.[210,211] Viruses in the herpesvirus group include herpes simplex, herpes zoster, Epstein-Barr virus, and cytomegalovirus (CMV). Cytomegalovirus remains one of the major infectious complications in renal transplantation, where the source of the virus may be the donor organ, blood transfusion, or reactivation of latent virus in the recipient.[212] Cytomegalovirus infections may be deleterious to graft survival and function and may cause substantial patient morbidity and mortality.[213] In most cases primary infections are more severe than reactivation of a latent virus, and both antilymphocyte globulin and OKT3 therapy can potentiate CMV infections.[113,214] It is now recognized that reinfection with a second virus strain may occur in seropositive recipients and that such patients are thus not immune to repeated primary CMV infections.[215] Reserving CMV-negative donors for CMV-negative recipients appears to be a useful preventive measure where practical but may add difficulty to transplant matching.[216-218] Efforts to develop an effective vaccine against CMV have been mostly disappointing,[219-221] but passive immunization with CMV hyperimmune globulin seems effective.[222] Prophylactic therapy with oral acyclovir after transplantation has reduced the incidence of primary CMV infection, and its use may reduce that of Epstein-Barr virus and herpesvirus infection as well as the incidence of Epstein-Barr-related lymphoproliferative disorders.[223] Because rapid diagnosis is critical, new and quicker tests to diagnose CMV infection are being introduced.[224-226] In addition, anti-CMV therapy has recently improved.[227] Whereas CMV lacks the virus-specific thymidine kinase needed for the phosphorylation and activation of acyclovir, newer agents such as ganciclovir are particularly active against CMV.[228-230] Other antiviral agents such as foscarnet[231] are also proving effective. There may be a role for combining therapy with hyperimmune globulin and ganciclovir in high-risk patients with serious infections.[232]

The herpes simplex virus can also be transmitted by the renal allograft,[233] but oral acyclovir has been used with good results to prevent herpes simplex infection in kidney transplant recipients.[234]

Transmission of the human immunodeficiency virus with the transplant organ or blood transfusion can occur despite the screening of donors.[235-237] Diagnosing the acquired immunodeficiency syndrome in persons with transplants may be more difficult, as antibody responses to HIV may be impaired.[238] Patients infected with HIV have a poor prognosis.[239,240] No patient with HIV antibodies should receive or donate an organ.[235] Patients with seroconversion after trans-

plantation should have their immunosuppression reduced, and possibly stopped, but they almost inevitably do poorly.[241]

*Malignancy*

The increased incidence of malignancy in patients receiving kidney transplants has been well documented[210,242] and is due to immunosuppressive therapy, viral infections, and occasionally to the transmission of cancer with the donor organs.[243] With increasing potency of immunosuppressive medication, the incidence of malignancy in transplant patients has increased.[244]

Skin cancer is the most common manifestation in some countries.[245,246] Epstein-Barr virus-related lymphoma has been of recent concern, and its appearance is associated with potent immunosuppression, especially with multiple drugs and high doses.[78,247,248] Some of these polyclonal lymphoproliferative states are responsive to acyclovir therapy combined with reduced immunosuppression.[249]

*Long-term Outcome*

The major causes of graft loss in the long term are chronic rejection and patient death. The predominant causes of death are infections, malignant neoplasms, and arteriovascular disease.[210,250,251]

When rejection takes place in long-surviving grafts, it is generally chronic or vascular pattern rejection, although acute rejection can also occur late.[252] Chronic rejection is poorly understood. It generally presents as a slow deterioration in renal function and less often as a sequence of episodes of renal impairment, but both respond poorly to antirejection therapy. Grafts with chronic rejection show progressive pruning of the distal arterial tree. A biopsy specimen shows a vascular pattern of rejection, with fibroblastic endothelial thickening of interlobular and arcuate arteries as well as glomerular and tubular ischemic changes.[253] While conventional theory holds that chronic rejection is predominantly antibody-mediated, evidence is growing that cellular immunity may play an important role.[254]

Chronic rejection is responsible for a significant proportion of late graft losses and contributes to a 3% to 10% annual late graft failure rate.[209,255] Among these losses must be counted grafts rejected because of poor patient compliance,[256,257] which may occur particularly in children and adolescents,[258] sometimes because of changes in appearance induced by therapy.[259,260] Glomerulopathy in kidney transplants may represent rejection, infection,[214] recurrent primary disease, or de novo glomerulonephritis. Some forms of glomerulonephritis, such as focal sclerosing glomerulonephritis,[261] IgA disease,[262] and membranoproliferative glomerulonephritis (type II), have a tendency to recur, often with deleterious consequences, and a proportion of patients go on to lose their grafts.[210,263,264] Immunosuppressive protocols including cyclosporine appear not to be effective in preventing the recurrence of glomerulonephritis in transplanted kidneys.[265]

## Future Directions

In the past decade there have been remarkable improvements in the understanding of the mechanisms of rejection and the actions of immunosuppressive agents. In conjunction with better management of infection and better patient care, these factors have been translated into better graft and patient survival after renal transplantation. It is now important to focus on the issues of patient well-being and the level of kidney function.

In the next decade further important advances in renal transplantation should occur, with an array of new immunosuppressive agents, better diagnostic abilities, and better antibiotics. The ability to induce specific transplant tolerance, with a reduction or elimination of the need for nonspecific immunosuppressive agents, has been shown in animal models and needs to be adapted to humans, as suggested by Strober and colleagues.[145] The ability to harness the immune system's own immunoregulatory processes to produce an acquired specific unresponsiveness to organ allografts could well eliminate many of the problems limiting the success of renal transplantation.

### REFERENCES


1. Kootte AM, Lensen LM, van Bockel JH, et al: High- and low-dose regimens of cyclosporin in renal transplantation: Immunosuppressive efficacy and side effects. Nephrol Dial Transplant 1988; 3:666-670

2. Najarian JS, Canafax DM, Sutherland DE: Renal transplantation in diabetic patients is confirmed therapy while pancreas transplantation should be performed only in an investigational setting. J Diabetic Complications 1988; 2:158-161

3. Ponticelli C, Tarantino A, Montagnino G, et al: A randomized trial comparing triple-drug and double-drug therapy in renal transplantation. Transplantation 1988; 45:913-918

4. Krensky AM, Suranyi MG, Clayberger C, et al: Advances in the immunobiology and clinical practice of transplantation. Curr Nephrol 1989; 13:417-465

5. Halloran PF, Cockfield SM, Madrenas J: The molecular immunology of transplantation and graft rejection. Immunol Allergy Clin North Am 1989; 9:1-20

6. Claas FH, Van Rood JJ: Transplantation in hyperimmunized patients. Adv Nephrol 1989; 18:317-323

7. Pirsch JD, Stratta RJ, Armbrust MJ, et al: Cadaveric renal transplantation with cyclosporine in patients more than 60 years of age. Transplantation 1989; 47:259-261

8. Shah B, First MR, Munda R, et al: Current experience with renal transplantation in older patients. Am J Kidney Dis 1988; 12:516-523

9. Läuffer G, Murie JA, Gray D, et al: Renal transplantation in patients over 55 years old. Br J Surg 1988; 75:984-987

10. Clark AGB, Rigden SPA, Haycock GB, et al: Renal transplantation in children. Transplant Rev (Orlando) 1987; 1:101-131

11. Kaufman DB, Sutherland DER, Fryd DS, et al: A single-center experience of renal transplantation in thirteen Jehovah's Witnesses. Transplantation 1988; 45:1045-1049

12. Smith AY, Van Buren CT, Lewis RM, et al: Short-term and long-term function of cadaveric kidneys from pediatric donors in recipients treated with cyclosporine. Transplantation 1988; 45:360-367

13. Fine RN: In depth review: Renal transplantation of the infant and young child and the use of pediatric cadaver kidneys for transplantation in pediatric and adult recipients. Am J Kidney Dis 1988; 12:1-10

14. Kasiske BL: The influence of donor age on renal function in transplant recipients. Am J Kidney Dis 1988; 11:248-253

15. Donnelly PK, Clayton DG, Simpson AR: Transplants from living donors in the United Kingdom and Ireland: A centre survey. Br Med J [Clin Res] 1989; 298:490-493

16. Tilney NL, Hollenberg NK: Use of living donors in renal transplantation. Transplant Rev (Orlando) 1987; 1:225-238

17. Pirsch JD, Sollinger HW, Kalayoglu M, et al: Living-unrelated renal transplantation: Results in 40 patients. Am J Kidney Dis 1988; 12:499-503

18. Bjorkman PJ, Saper MA, Samraoui B, et al: The foreign antigen binding site and T-cell recognition regions of class I histocompatibility antigens. Nature 1987; 329:512-523

19. Albert ED: What is new in HLA in 1988? Transplant Rev (Orlando) 1988; 2:207-219

20. Kaufman DB, Sutherland DER, Noreen H, et al: Renal transplantation between living-related sibling pairs matched for zero-HLA haplotypes. Transplantation 1989; 47:113-119

21. Lewis RM, Janney RP, Golden DL, et al: Stability of renal allograft function associated with long-term cyclosporine immunosuppressive therapy—Five-year follow-up. Transplantation 1989; 47:266-272

22. Takiff H, Cook D, Himaya N, et al: Dominant effect of histocompatibility on ten-year kidney transplant survival. Transplantation 1988; 45:410-415

23. Wynn JJ, Pfaff WW, Patton PR, et al: Late results of renal transplantation. Transplantation 1988; 45:329-333

24. Opelz G: Influence of HLA matching on survival of second kidney transplants in cyclosporine-treated recipients. Transplantation 1989; 47:823-827

25. Gilks WR, Bradley BA, Gore SM, et al: Substantial benefits of tissue matching in renal transplantation. Transplantation 1987; 43:669-674

26. Opelz G: The benefit of exchanging donor kidneys among transplant centers. N Engl J Med 1988; 318:1289-1292

27. Takiff H, Iwaki Y, Cecka M, et al: The benefit and underutilization of sharing kidneys for better histocompatibility. Transplantation 1989; 47:102-105

28. Cicciarelli J, Terasaki PI, Mickey MR: The effect of zero HLA class I and II mismatching in cyclosporine-treated kidney transplant patients. Transplantation 1987; 43:636-640

29. Hunsicker LG: Renal transplantation for the nephrologist: HLA matching and cadaveric kidney allocation (Editorial). Am J Kidney Dis 1989; 13:438-441

30. Salvatierra O: Optimal use of organs for transplantation. N Engl J Med 1988; 318:1329-1331

31. Alexander JW, Vaughn WK, Pfaff WW: Local use of kidneys with poor HLA matches is as good as shared use with good matches in the cyclosporine era: An analysis at one and two years. Transplant Proc 1987; 19:672-674

32. Hoffmann RM, Stratta RJ, D'Alessandro AM, et al: Combined cold storage perfusion preservation with a new synthetic perfusate. Transplantation 1989; 47:32-37

33. McAnulty JF, Ploeg RJ, Southard JH, et al: Successful five-day perfusion preservation of the canine kidney. Transplantation 1989; 47:37-41

34. Henry ML, Sommer BG, Ferguson RM: Improved immediate function of renal allografts with Belzer perfusate. Transplantation 1988; 45:73-75

35. Belzer FO, Southard JH: Principles of solid-organ preservation by cold storage. Transplantation 1988; 45:673-676

36. O'Brien BJ: A game-theoretic approach to donor kidney sharing. Soc Sci Med 1988; 26:1109-1116

37. Burlingham WJ, Stratta R, Mason B, et al: Risk factors for sensitization by blood transfusions. Transplantation 1989; 47:140-144

38. Scornik JC, Salomon DR, Lim PB, et al: Posttransplant antidonor antibodies and graft rejection—Evaluation by two-color flow cytometry. Transplantation 1989; 47:287-290

39. Baldwin WM, Paul LC, Claas FH, et al: Destructive and protective effects of antibody on transplants in humans: Practical and theoretical considerations. Prog Clin Biol Res 1986; 224:41-57

40. Carpenter CB, Milford EL: HLA matching in cadaveric renal transplantation. Immunol Allergy Clin North Am 1989; 9:45-60

41. Taylor CJ, Chapman JR, Fuggle SV, et al: A positive B-cell crossmatch due to IgG anti-HLA-DQ antibody present at the time of transplantation in a successful renal allograft. Tissue Antigens 1987; 30:104-112

42. Talbot D, Givan AL, Shenton BK, et al: The relevance of a more sensitive crossmatch assay to renal transplantation. Transplantation 1989; 47:552-555

43. Talbot D, Givan AL, Shenton BK, et al: Rapid detection of low levels of donor specific IgG by flow cytometry with single and dual colour fluorescence in renal transplantation. J Immunol Methods 1988; 112:279-283

44. Lazda VA, Pollak R, Mozes MF, et al: The relationship between flow cytometer crossmatch results and subsequent rejection episodes in cadaver renal allograft recipients. Transplantation 1988; 45:562-565

45. Stratta RJ, Mason B, Lorentzen DF, et al: Cadaveric renal transplantation with quadruple immunosuppression in patients with a positive antiglobulin crossmatch. Transplantation 1989; 47:282-286

46. Joyce S, Flye MW, Mohanakumar T: Characterization of kidney cell-specific, non-major histocompatibility complex alloantigen using antibodies eluted from rejected human renal allografts. Transplantation 1988; 46:362-369

47. Evans PR, Trickett LP, Gosney AR, et al: Detection of kidney-reactive antibodies at crossmatch in renal transplant recipients. Transplantation 1988; 46:844-852

48. Cerilli J, Clarke J, Doolin T, et al: The significance of a donor-specific vessel crossmatch in renal transplantation. Transplantation 1988; 46:359-361

49. Weir MR, Shen SY, Dagher FJ, et al: Brief communications: Effects of allostimulation and cyclosporine therapy on cytotoxic antibody production in highly sensitized prospective renal transplant recipients. Transplantation 1988; 46:591-593

50. Claas FH, Gijbels Y, van Der Velden-de Munck J, et al: Induction of B cell unresponsiveness to noninherited maternal HLA antigens during fetal life. Science 1988; 241:1815-1817

51. Matas AJ, Tellis VA, Quinn TA, et al: Successful transplantation of highly sensitized patients without regard to HLA matching. Transplantation 1988; 45:338-342

52. Taube D, Palmer A, Welsh K, et al: Removal of anti-HLA antibodies prior to transplantation: An effective and successful strategy of highly sensitized renal allograft recipients. Transplant Proc 1989; 21:694-695

53. Palmer A, Taube D, Welsh K, et al: Removal of anti-HLA antibodies by extracorporeal immunoadsorption to enable transplantation. Lancet 1989; 1:10-12

54. Opelz G, Sengar DP, Mickey MR, et al: Effect of blood transfusions on subsequent kidney transplants. Transplant Proc 1973; 5:253-259

55. Cochrum KC, Hanes D, Potter D, et al: Donor-specific blood transfusions in HLA-D disparate one-haplotype related allografts. Transplant Proc 1979; 11:1903-1907

56. Pfaff WW, Howard RJ, Scornik JC, et al: Incidental and purposeful random donor blood transfusion—Sensitization and transplantation. Transplantation 1989; 47:130-133

57. Burlingham WJ, Grailer A, Sondel PM, et al: Improved renal allograft survival following donor-specific transfusions—III. Kinetics of mixed lymphocyte responses before and after transplantation. Transplantation 1988; 45:127-132

58. Opelz G: Improved kidney graft survival in nontransfused recipients. Transplant Proc 1987; 19:149-152

59. Eschbach JW: Nephrology forum: The anemia of chronic renal failure: Pathophysiology and the effects of recombinant erythropoietin. Kidney Int 1989; 35:134-148

60. Scornik JC, Salomon RJ, Pfaff WW: Prevention of transfusion-induced broad sensitization in renal transplant candidates. Transplantation 1989; 47:617-620

61. Opelz G: To transfuse or not before transplantation. Transplant Rev (Orlando) 1988; 2:77-85

62. Kim TH, Shank BM, Vallera DA, et al: Immunosuppressive techniques using radiation. Am J Clin Oncol 1988; 11:362-367

63. Yadav RVS, Indudhara R, Kumar P, et al: Cyclophosphamide in renal transplantation. Transplantation 1988; 45:421-424

64. Thorogood J, Van Houwelingen JC, Van Rood JJ, et al: Time trend in annual kidney graft survival. Transplantation 1988; 46:686-690

65. Simmons RG, Abress L, Anderson CR: Quality of life after kidney transplantation—A prospective, randomized comparison of cyclosporine and conventional immunosuppressive therapy. Transplantation 1988; 45:415-421

66. Rees L, Greene SA, Adlard P, et al: Growth and endocrine function after renal transplantation. Arch Dis Child 1988; 63:1326-1332

67. Bishop GA, Hall BM: Effects of immunosuppressive drugs on functions of activated T lymphocytes—Cyclosporine inhibition of gamma interferon production in the presence of interleukin. Transplantation 1988; 45:967-972

68. McKenna RM, Szturm K, Jeffery JR, et al: Inhibition of cytokine production by cyclosporine A and G. Transplantation 1989; 47:343-348

69. Foxwell BMJ, Ryffel B: The mechanisms of action of cyclosporine. Immunol Allergy Clin North Am 1989; 9:79-93

70. Henry ML, Bowers VD, Sommer BG, et al: Combination drug therapies for immunosuppression in renal transplantation. Transplant Rev (Orlando) 1988; 2:55-76

71. Hall BM, Tiller DJ, Hardie I, et al: Comparison of three immunosuppressive regimens in cadaver renal transplantation: Long-term cyclosporine, short-term cyclosporine followed by azathioprine and prednisolone, and azathioprine and prednisolone without cyclosporine. N Engl J Med 1988; 318:1499-1507

72. Vanderwerf BA, Serota AI: Low-dose cyclosporine for cadaveric renal transplantation. Transplantation 1988; 45:320-323

73. Stratta RJ, Armbrust MJ, Oh CS, et al: Withdrawal of steroid immunosuppression in renal transplant recipients. Transplantation 1988; 45:323-328

74. Kupin W, Venkat KK, Oh HK, et al: Complete replacement of methylprednisolone by azathioprine in cyclosporine-treated primary cadaveric renal recipients. Transplantation 1988; 45:53-55

75. Hall BM, Tiller DJ, Duggin GG, et al: Post-transplant acute renal failure in cadaver renal recipients treated with cyclosporine. Kidney Int 1985; 28:178-186

76. D'Alessandro AM, Pirsch JD, Stratta RJ, et al: OKT3 salvage therapy in quadruple immunosuppressive protocol in cadaveric renal transplantation. Transplantation 1988; 47:297-300

77. Stratta RJ, Sollinger HW, D'Alessandro AM, et al: Experience with quadruple immunosuppressive therapy in renal transplants. Immunol Allergy Clin North Am 1989; 9:109-135

78. Wilkinson AH, Smith JL, Hunsicker LG, et al: Increased frequency of post-transplant lymphomas in patients treated with cyclosporine, azathioprine and prednisone. Transplantation 1989; 47:293-296

79. Higgins RM, Bloom SL, Hopkin JM, et al: The risks and benefits of low-dose cotrimoxazole prophylaxis for *Pneumocystis* pneumonia in renal transplantation. Transplantation 1989; 47:558-560

80. Keown PA, Optimizing cyclosporine therapy: Dose, levels and monitoring. Transplant Proc 1988; 20(suppl 2):382-389

81. Sgoutas DS, Hammarstrom M: Comparison of specific radioimmunoassays for cyclosporine. Transplantation 1989; 47:668-670

82. Cantarovich F, Bizollon C, Cantarovich D, et al: Cyclosporine plasma levels six hours after oral administration—A useful tool for monitoring therapy. Transplantation 1988; 45:389-394

83. Schroeder TJ, Brunson ME, Pesce AJ, et al: A comparison of the clinical utility of the radioimmunoassay, high-performance liquid chromatography, and TDx cyclosporine assays in outpatient renal transplant recipients. Transplantation 1989; 47:262-266

84. Chapman JR, Morris PJ: Cyclosporine conversion. Transplant Rev (Orlando) 1987; 1:197-224

85. Myers BD, Newton L, Boshkos C, et al: Chronic injury of human renal microvessels with low-dose cyclosporine therapy. Transplantation 1988; 46:694-703

86. Hoitsma AJ, Wetzels JFM, van Lier HJJ, et al: Cyclosporin treatment with conversion after three months versus conventional immunosuppression in renal allograft recipients. Lancet 1987; 1:584-586

87. Kootte AM, Lensen LM, Van Es LA, et al: Controlled cyclosporine conversion at three months after renal transplantation. Transplantation 1988; 46:677-680

88. Shen SY, Weir MW, Couglin TR: Renal allograft biopsy and conversion of cyclosporine to azathioprine. Transplantation 1989; 47:223-229

89. Gonwa TA, Nghiem DD, Schulak JA, et al: Results of conversion from cyclosporine to azathioprine in cadaveric renal transplantation. Transplantation 1987; 43:225-228

90. Rosenblum ND, Harmon WE, Levey RH: Brief communications: Treatment of chronic renal allograft rejection with cyclosporine and prednisone. Transplantation 1988; 45:232-234

91. Matas AJ, Tellis VA, Quinn TA, et al: Individualization of immediate post-transplant immunosuppression—The value of antilymphocyte globulin in patients with delayed graft function. Transplantation 1988; 45:406-409

92. Waldmann H: Monoclonal antibodies for organ transplantation: Prospects for the future. Am J Kidney Dis 1988; 11:154-158

93. Kirkman RL, Araujo JL, Busch GJ, et al: Treatment of acute renal allograft rejection with monoclonal anti-T12 antibody. Transplantation 1983; 36:620-626

94. Hall BM: Therapy with monoclonal antibodies to CD4: Potential not appreciated? Am J Kidney Dis 1989; 14(suppl 2):71-77

95. Aversa GG, Suranyi MG, Waugh JA, et al: Detection of late lymphocyte activation marker by A1, a new monoclonal antibody. Transplant Proc 1988; 20:49-52

96. Didlake RH, Kim EK, Sheehan K, et al: Brief communications: Effect of combined anti-γ interferon antibody and cyclosporine therapy on cardiac allograft survival in the rat. Transplantation 1988; 45:222-223

97. Iwai H, Kuma SI, Inaba MM, et al: Acceptance of murine thyroid allografts by pretreatment of anti-Ia antibody or anti-dendritic cell antibody in vitro. Transplantation 1989; 47:45-49

98. Norman DJ: The clinical role of OKT3. Immunol Allergy Clin North Am 1989; 9:95-107

99. Weimar W, Baumgartner D, Hendriks GF, et al: The prophylactic use of Orthoclone OKT3 in kidney and heart transplantation. Transplant Proc 1988; 20(suppl 6):96-100

100. Debure A, Chkoff N, Chatenoud L, et al: One-month prophylactic use of OKT3 in cadaver kidney transplant recipients. Transplantation 1988; 45:546-553

101. Stratta RJ, D'Alessandro AM, Hoffmann RM, et al: Cadaveric renal transplantation in the cyclosporine and OKT3 eras. Surgery 1988; 104:606-615

102. Norman DJ, Shield CF, Barry JM, et al: Therapeutic use of OKT3 monoclonal antibody for acute renal allograft rejection. Nephron 1987; 46(suppl 1):41-47

103. Fung JJ, Demetris AJ, Porter KA, et al: Use of OKT3 with ciclosporin and steroids for reversal of acute kidney and liver allograft rejection. Nephron 1987; 46(suppl 1):19-39

104. Ortho Multicenter Transplant Study Group: A randomized clinical trial of OKT3 monoclonal antibody for acute rejection of cadaveric renal transplants. N Engl J Med 1985; 313:337-342

105. Goldstein G: Monoclonal antibody specificity: Orthoclone OKT3 T-cell blocker. Nephron 1987; 46(suppl 1):5-11

106. Kahana L, Baxter J: OKT3 rescue in refractory renal rejection. Nephron 1987; 46(suppl 1):34-40

107. Norman DJ, Barry JM, Bennett WM, et al: The use of OKT3 in cadaveric renal transplantation for rejection that is unresponsive to conventional anti-rejection therapy. Am J Kidney Dis 1988; 11:90-93

108. Rubin MF, Nghiem DD, Stachura I: Late steroid-resistant rejection response to OKT3. Transplantation 1988; 45:818-819

109. Delaney VB, Campbell WG, Nasr SA, et al: Efficacy of OKT3 monoclonal antibody therapy in steroid-resistant, predominantly vascular acute rejection. Transplantation 1988; 45:743-748

110. Cosimi AB: OKT3: First-dose safety and success. Nephron 1987; 46(suppl 1):12-18

111. Abramowicz D, Schandene L, Goldman M, et al: Release of tumor necrosis factor, interleukin-2 and gamma interferon in serum after injection of OKT3 monoclonal antibody in kidney transplant recipients. Transplantation 1989; 47:606-608

112. Debets JM, Leunissen KM, Van Hooff HJ, et al: Evidence of involvement of tumor necrosis factor in adverse reactions during treatment of kidney allograft rejection with antithymocyte globulin. Transplantation 1989; 47:487-492

113. Oh CS, Stratta RF, Fox BC, et al: Increased infections associated with the use of OKT3 for treatment of steroid-resistant rejection in renal transplantation. Transplantation 1988; 45:68-73

114. Chou S, Norman DJ: Effect of OKT3 antibody therapy on cytomegalovirus reactivation in renal transplant recipients. Transplant Proc 1985; 17:2755-2756

115. Lazarovits AI, Shield CF: Recurrence of acute rejection in the absence of CD3-positive lymphocytes. Clin Immunol Immunopathol 1988; 48:392-400

116. Shield CF III, Norman DJ, Marlett P, et al: Comparison of antimouse and antihorse antibody production during the treatment of allograft rejection with OKT3 or antithymocyte globulin. Nephron 1987; 46(suppl 1):48-51

117. Chatenoud L, Jonker M, Villemain F, et al: The human immune response to the OKT3 monoclonal antibody is oligoclonal. Science 1986; 232:1406-1408

118. Norman DJ, Shield CF III, Henell KR, et al: Effectiveness of a second course of OKT3 monoclonal anti-T cell antibody for treatment of renal allograft rejection. Transplantation 1988; 46:523-529

119. First MR, Schroeder TJ, Hurtubise PE, et al: Successful retreatment of allograft rejection with OKT3. Transplantation 1989; 47:88-91

120. Mayes JT, Thistlethwaite JR, Stuart JK, et al: Reexposure to OKT3 in renal allograft recipients. Transplantation 1988; 45:349-353

121. Shield CF, Hughes JD, Marlett P, et al: The human anti-mouse response to OKT3—Crossreactive pattern analysis using a large group of anti-CD3 and isotypic monoclonal antibodies. Transplant Proc 1989; 21:981-984

122. Hirsch R, Chatenoud L, Gress RE, et al: Suppression of the humoral response to anti-CD3 monoclonal antibody. Transplantation 1989; 47:853-857

123. Paetkau V, Mills GB: Cytokines and mechanisms of lymphocyte activation. Immunol Allergy Clin North Am 1989; 9:21-43

124. Strom TB, Kelley VE: Toward more selective therapies to block undesired immune responses. Kidney Int 1989; 35:1026-1033

125. Diamantstein T, Osawa H, Kirkman RL, et al: Interleukin 2 receptor—A target for immunosuppressive therapy. Transplant Rev (Orlando) 1987; 1:177-196

126. Soulillou JP, Peyronnet P, Le Mauff B, et al: Prevention of rejection of kidney transplants by monoclonal antibody directed against interleukin 2. Lancet 1987; 1:1339-1342

127. Kupiec-Weglinski JW, Diamantstein T, Tilney NL: Interleukin 2 receptor-targeted therapy—Rationale and applications in organ transplantation. Transplantation 1988; 46:785-792

128. Cantarovich D, Le Mauff B, Hourmant M, et al: Anti-interleukin 2 receptor monoclonal antibody in the treatment of ongoing acute rejection episodes in human kidney graft—A pilot study. Transplantation 1989; 47:454-457

129. Turka LA, Carpenter CB, Yunis EJ, et al: Selective sparing of suppressor cells generated in mixed lymphocyte response by an anti-interleukin-2 receptor antibody. Transplantation 1989; 47:182-188

130. Murphy JR, Kelley VE, Strom TB: Interleukin 2 toxin: A step toward selective immunomodulation. Am J Kidney Dis 1988; 11:159-162

131. Pankewycz O, Mackie J, Hassarjian R, et al: Interleukin-2-diphtheria toxin fusion protein prolongs murine islet cell engraftment. Transplantation 1989; 47:318-322

132. Kirkman RL, Bacha P, Barrett LV, et al: Prolongation of cardiac allograft survival in murine recipients treated with a diphtheria toxin-related interleukin-2 fusion protein. Transplantation 1989; 47:327-330

133. Tejani A, Lancman I, Pomrantz A, et al: Nephrotoxicity of cyclosporine A and cyclosporine G in a rat model. Transplantation 1988; 45:184-187

134. Yoshimura N, Matsui S, Hamashima T, et al: Effect of a new immunosuppressive agent, FK506, on human lymphocyte responses in vitro—I. Inhibition of expression of alloantigen-activated suppressor cells, as well as induction of alloreactivity. Transplantation 1989; 47:351-356

135. Yoshimura N, Matsui S, Hamashima T, et al: Effect of a new immunosuppressive agent, FK506, on human lymphocyte responses in vitro—II. Inhibition of the production of IL-2 and $\gamma$-IFN, but not B cell-stimulating factor 2. Transplantation 1989; 47:356-359

136. Warty V, Diven W, Cadoff E, et al: Brief communications: FK506: A novel immunosuppressive agent—Characteristics of binding and uptake by human lymphocytes. Transplantation 1988; 46:453-455

137. Thomson W: FK-506—How much potential? Immunol Today 1989; 10:6-9

138. Tuch BE, Lissing JE, Suranyi MG: Immunomodulation of human fetal cells by the fungal metabolite gliotoxin. Immunol Cell Biol 1988; 66:307-312

139. Oesterwitz H, Scholz D, Kaden J, et al: Photochemical donor pretreatment in clinical kidney transplantation—Preliminary report. Urol Res 1987; 15:211-213

140. Pollack MS, Short HD III, Young JB, et al: Brief communications: Graft stability in a heart transplant recipient whose immunosuppressive therapy was discontinued for 8 months. Transplantation 1988; 45:242-243

141. Hall BM: Tolerance and specific unresponsiveness in organ transplantation. Immunol Allergy Clin North Am 1989; 9:61-77

142. Barber WH, Diethelm A, Laskow DA, et al: Use of cryopreserved donor bone marrow in cadaver kidney allograft recipients. Transplantation 1989; 47:66-71

143. Myburgh JA, Meyers AM, Thomson PD, et al: Total lymphoid irradiation—Current status. Transplant Proc 1989; 21:826-828

144. Chow D, Saper V, Strober S: Renal transplant patients treated with total lymphoid irradiation show specific unresponsiveness to donor antigens in the mixed leukocyte reaction (MLR). J Immunol 1987; 138:3746-3750

145. Strober S, Dhillon M, Schubert M, et al: Acquired immune tolerance to cadaveric renal allografts. N Engl J Med 1989; 321:28-33

146. Saper V, Chow D, Engleman ED, et al: Clinical and immunological studies of cadaveric renal transplant recipients given total-lymphoid irradiation and maintained on low-dose prednisone. Transplantation 1988; 45:540-546

147. Pahl MV, Barton CH, Ulich T, et al: Nephrology consultant: Renal dysfunction and microangiopathic changes in a renal transplant patient. Am J Nephrol 1988; 8:72-79

148. Hall BM: Cellular infiltrates in allografts. Transplant Proc 1987; 19:50-56

149. Waltzer WC, Miller F, Arnold A, et al: Value of percutaneous core needle biopsy in the differential diagnosis of renal transplant dysfunction. J Urol 1987; 137:1117-1121

150. Bishop GA, Hall BM, Duggin GG, et al: Immunopathology of renal allograft rejection analyzed with monoclonal antibodies to mononuclear markers. Kidney Int 1986; 29:708-717

151. Colvin RB: Diagnostic use in transplantation: Clinical applications of monoclonal antibodies in renal allograft biopsies. Am J Kidney Dis 1988; 11:126-130

152. Hall BM, Bishop GA, Duggin GG, et al: Increased expression of HLA-DR antigens on renal tubular cells in renal transplants: Relevance to the rejection response. Lancet 1984; 2:247-251

153. Häyry P, von Willebrand E, Ahonen J, et al: Aspiration cytology in organ transplantation. Transplant Rev (Orlando) 1987; 1:133-157

154. Bishop GA, Hall BM, Waugh J, et al: Diagnosis of renal allograft rejection by analysis of fine-needle aspiration biopsy specimens with immunostains and simple cytology. Lancet 1986; 2:645-650

155. Tötterman TH, Hanås E, Bergström R, et al: Immunologic diagnosis of kidney rejection using FACS analysis of graft-infiltrating functional and activated T and NK cell subsets. Transplantation 1989; 47:817-823

156. Dunbar KR, Salomon DR, Kaude J, et al: Loss of corticomedullary demarcation on magnetic resonance imaging: An index of biopsy-proven acute renal transplant dysfunction. Am J Kidney Dis 1988; 12:200-207

157. Van Gansbake D, Segebarth C, Toussaint C, et al: Non-obstructive kidney transplant dysfunction: Magnetic resonance evaluation. Br J Radiol 1988; 61:473-491

158. Te Strake L, Schultze Kool LJ, Paul LC, et al: Magnetic resonance imaging of renal transplants: Its value in the differentiation of acute rejection and cyclosporin A neprhrotoxicity. Clin Radiol 1988; 38:220-228

159. Dubovsky FV, Russell CDJ: Radionuclide evaluation of renal transplants. Semin Nucl Med 1988; 18:181-198

160. Goldsmith MS, Tanasescu DE, Waxman AD, et al: Comparison of magnetic resonance imaging and radionuclide imaging in the evaluation of renal transplant failure. Clin Nucl Med 1988; 13:250-257

161. Hall JT, Kim EE, Pjura GA, et al: Correlation of radionuclide and ultrasound studies with biopsy findings for the diagnosis of renal transplant rejection. Urology 1988; 32:172-179

162. Buckley AR, Cooperberg PL, Reeve CE, et al: The distinction between acute renal transplant rejection and cyclosporine nephrotoxicity: Value of duplex sonography. AJR 1987; 149:521-525

163. Gankins SM, Sanfilippo FP, Carroll RA: Duplex doppler sonography of renal transplants: Lack of sensitivity and specificity in established pathologic diagnosis. AJR 1989; 152:535-539

164. Allen KS, Jorkasky DK, Arger PH, et al: Renal allografts: Prospective analysis of Doppler sonography. Radiology 1988; 169:371-376

165. Foxwell BMJ, Ryffel B: The mechanisms of action of cyclosporine. Immunol Allergy Clin North Am 1989; 9:79-93

166. Sommer BG, Sing DE, Henry ML, et al: Serum cyclosporine kinetic profile—Failure to correlate with nephrotoxicity or rejection episodes following sequential immunotherapy for renal transplantation. Transplantation 1988; 45:86-90

167. Mihatsch MJ, Steiner K, Abeywickrama KH, et al: Risk factors for the development of chronic cyclosporine nephrotoxicity. Clin Nephrol 1988; 29:165-175

168. Moyer TP, Post GR, Sterioff S, et al: Cyclosporine nephrotoxicity is minimized by adjusting dosage on the basis of drug concentration in blood. Mayo Clin Proc 1988; 63:241-247

169. Lorber MI, Flechner SM, Van Buren CT, et al: Cyclosporine toxicity: The

effect of combined therapy using cyclosporine, azathioprine, and prednisone. Am J Kidney Dis 1987; 6:476-484

170. Rocher LL, Hodgson RJ, Merion RM, et al: Amelioration of chronic renal allograft dysfunction in cyclosporine-treated patients by addition of azathioprine. Transplantation 1989; 47:249-254

171. Nahman DS, Cosio FG, Kolkin S, et al: Cyclosporine nephrotoxicity without major organ transplantation. Ann Intern Med 1987; 106:400-402

172. Ontario Renal Transplant Research Group: Factors influencing early renal function in cadaveric kidney transplants—A case control study. Transplantation 1988; 45:122-127

173. Canadian Multicenter Transplant Study Group: A randomized clinical trial of cyclosporine in cadaveric renal transplantation. N Engl J Med 1983; 309:809-815

174. Halloran PF, Aprile MW, Farewell V, et al: Early function as the principal correlate of graft survival—A multivariate analysis of 200 cadaveric renal transplants treated with a protocol incorporating antilymphocyte globulin and cyclosporine. Transplantation 1988; 46:223-228

175. Sommer BG, Henry MC, Ferguson RM: Sequential antilymphoblast globulin and cyclosporine for renal transplantation. Transplantation 1987; 43:85-90

176. Golub MS, Berger ME: Direct augmentation by cyclosporine A of the vascular contractile response to nerve stimulation. Hypertension 1987; 9(pt 2)III:96-100

177. Curtis JJ, Luke RG, Dubovsky E, et al: Cyclosporin in therapeutic doses increases renal allograft vascular resistance. Lancet 1986; 2:477-479

178. English J, Evan A, Houghton DC, et al: Cyclosporine-induced renal dysfunction in the rat: Evidence for arteriolar vasoconstriction with preservation of tubular function. Transplantation 1987; 44:135-141

179. Remuzzi G, Bertani T: In-depth review: Renal vascular and thrombotic effects of cyclosporine. Am J Kidney Dis 1989; 13:261-272

180. Bennett WM: Basic mechanisms and pathophysiology of cyclosporine nephrotoxicity. Transplant Proc 1985; 17:297-302

181. Rogers TS, Elzinga L, Bennett WM, et al: Selective enhancement of thromboxane in macrophages and kidneys in cyclosporine-induced nephrotoxicity—Dietary protection by fish oil. Transplantation 1988; 45:153-156

182. Petric R, Freeman D, Wallace C, et al: Effect of cyclosporine on urinary prostanoid excretion, renal blood flow and glomerulotubular function. Transplantation 1988; 45:883-889

183. Voss BL, Hamilton KK, Samara ENS, et al: Cyclosporine suppression of endothelial prostacyclin generation. Transplantation 1988; 45:793-796

184. Coffman TM, Carr DR, Yarger WE, et al: Evidence that renal prostaglandin and thromboxane production is stimulated in chronic cyclosporine nephrotoxicity. Transplantation 1987; 43:282-285

185. Perico N, Benigni A, Zoja C, et al: Functional significance of exaggerated renal thromboxane $A_2$ synthesis induced by cyclosporin A. Am J Physiol 1986; 251 (pt 2):F581-587

186. Elzinga L, Kelley V, Houghton DC, et al: Fish oil modifies experimental cyclosporine nephrotoxicity and decreases renal prostaglandins. Transplantation 1987; 43:271-273

187. Baciewicz AM, Baciewicz FA: Cyclosporine pharmacokinetic drug interactions. Am J Surg 1989; 157:264-271

188. Barros EJG, Boim MA, Ajzen H, et al: Glomerular hemodynamics and hormonal participation on cyclosporine nephrotoxicity. Kidney Int 1987; 32:19-25

189. Handschumacher RE, Harding MW, Rice J, et al: Cyclophilin: A specific cytosolic binding protein for cyclosporin A. Science 1984; 226:544-547

190. Lewis RM, Janney RP, Golden DL, et al: Stability of renal allograft function associated with long-term cyclosporine immunosuppressive therapy—Five-year follow-up. Transplantation 1989; 47:266-272

191. Myers BD, Sibley R, Newton L, et al: The long-term course of cyclosporine-associated chronic nephropathy. Kidney Int 1988; 33:590-600

192. McDiarmid SV, Ettenger RB, Fine RN, et al: Serial decrease in glomerular filtration rate in long-term pediatric liver transplantation survivors treated with cyclosporine. Transplantation 1989; 47:314-318

193. Ruiz P, Kolbeck PC, Scroggs MW, et al: Associations between cyclosporine therapy and interstitial fibrosis in renal allograft biopsies. Transplantation 1988, 45: 91-95

194. Canadian Multicentre Transplant Study Group: A randomized clinical trial of cyclosporine in cadaveric renal transplantation: Analysis at three years. N Engl J Med 1986; 314:1219-1225

195. Tomlanovich S, Golbetz H, Perlroth M, et al: Limitations of creatinine in quantifying the severity of cyclosporine-induced chronic nephropathy. Am J Kidney Dis 1986; 8:332-337

196. Curtis JJ: Hypertension in the renal transplant patient. Transplant Rev (Orlando) 1988; 2:17-28

197. Luke RG: Nephrology forum: Hypertension in renal transplant recipients. Kidney Int 1987; 31:1024-1037

198. Chapman JR, Marcen R, Arias M, et al: Hypertension after renal transplantation—A comparison of cyclosporine and conventional immunosuppression. Transplantation 1987; 43:860-864

199. Rosansky SJ, Sugimoto T: An analysis of the United States renal transplant patient population and organ survival characteristics: 1977 to 1980. Kidney Int 1982; 22:685-692

200. McGeown MG, Douglas JF, Donaldson RA, et al: Ten-year results of renal transplantation with azathioprine and prednisolone as only immunosuppression. Lancet 1988; 1:983-985

201. Cheigh JS, Haschemeyer RH, Wang JCL, et al: Hypertension in kidney transplant recipients—Effect on long-term renal allograft survival. Am J Hypertens 1989; 2(pt 1):341-348

202. Curtis JJ, Luke RG, Diethelm AG, et al: Benefits of removal of native kidneys in hypertension after renal transplantation. Lancet 1985; 2:739-742

203. Linas SL, Miller PD, McDonald KM, et al: Role of the renin-angiotensin system in post-transplantation hypertension in patients with multiple kidneys. N Engl J Med 1978; 298:1440-1444

204. Thompson ME, Shapiro AP, Johnsen AM, et al: The contrasting effects of cyclosporin-A and azathioprine on arterial blood pressure and renal function following cardiac transplantation. Int J Cardiol 1986; 11:219-229

205. Palestine AG, Nussenblatt RB, Chan CC: Side effects of systemic cyclosporine in patients not undergoing transplantation. Am J Med 1984; 77:652-656

206. Myers BD: Cyclosporine nephrotoxicity. Kidney Int 1986; 30:964-974

207. Von Graffenried B, Krupp P: Side effects of cyclosporine in renal transplant recipients and in patients with autoimmune diseases. Transplant Proc 1986; 18:876-883

208. Curtis JJ, Luke RG, Jones P, et al: Hypertension in cyclosporine-treated renal transplant recipients is sodium dependent. Am J Med 1988; 85:134-138

209. Forman SJ, Textor SC, Carlson JE: Prednisone potentiates cyclosporine-induced blood pressure changes in normotensive bone marrow transplant recipients (Abstr). Kidney Int 1987; 31:297

210. Mahony JF, Sheil AGR: Long-term complications of cadaver renal transplantation. Transplant Rev (Orlando) 1987; 1:47-58

211. Ho M, Jaffe R, Miller G, et al: The frequency of Epstein-Barr virus infection and associated lymphoproliferative syndrome after transplantation and its manifestations in children. Transplantation 1988; 45:719-727

212. Preiksaitis JK: Cytomegalovirus infection in transplant recipients. Immunol Allergy Clin North Am 1989; 9:137-151

213. Lewis RM, Johnson PC, Golden D, et al: The adverse impact of cytomegalovirus infection on clinical outcome in cyclosporine-prednisone treated renal allograft recipients. Transplantation 1988; 45:353-359

214. Boyce NW, Hayes K, Gee D, et al: Cytomegalovirus infection complicating renal transplantation and its relationship to acute transplant glomerulopathy. Transplantation 1988; 45:706-709

215. Grundy JE, Lui SF, Super M, et al: Symptomatic cytomegalovirus infection in seropositive kidney recipients: Reinfection with donor virus rather than reactivation of recipient virus. Lancet 1988; 2:132-135

216. Weir MR, Henry ML, Blackmore M, et al: Incidence and morbidity of cytomegalovirus disease associated with a seronegative recipient receiving seropositive donor-specific transfusion and living-related donor transplantation. Transplantation 1988; 45:111-116

217. Johnson PC, Lewis RM, Golden DL, et al: The impact of cytomegalovirus infection on seronegative recipients of seropositive donor kidneys versus seropositive recipients treated with cyclosporine-prednisone immunosuppression. Transplantation 1988; 45:116-121

218. Metselaar HJ, Ploeg RJ, Van Loon AM, et al: Prevention of CMV infection by screening for CMV antibodies in renal allograft recipients and the blood and kidney donors. Scand J Infect Dis 1988; 20:135-139

219. Balfour HH, Welo PK, Sachs GW: Cytomegalovirus vaccine trial in 400 renal transplant candidates. Transplant Proc 1985; 17:81-83

220. Farrar GH, Bull JR, Greenaway PJ: Prospects for the clinical management of human cytomegalovirus infections. Vaccine 1986; 4:217-224

221. Brayman KL, Dafoe DC, Smythe WR, et al: Prophylaxis of serious cytomegalovirus infection in renal transplant candidates using live human cytomegalovirus vaccine—Interim results of a randomized trial. Arch Surg 1988; 123:1502-1508

222. Syndman DR, Werner BG, Tilney NL, et al: A further analysis of primary cytomegalovirus disease prevention in renal transplant recipients with a cytomegalovirus immune globulin: Interim comparison of a randomized and an open-label trial. Transplant Proc 1988; 20(suppl 8):24-30

223. Balfour HH, Chace BA, Stapleton JT, et al: A randomized placebo-controlled trial of oral acyclovir for the prevention of cytomegalovirus disease in recipients of renal allografts. N Engl J Med 1989; 320:1381-1387

224. Van der Bij W, Schirm J, Torensma R, et al: Comparison between viremia and antigenemia for detection of cytomegalovirus in blood. J Clin Microbiol 1988; 26:2531-2535

225. Kemnitz J, Haverich A, Gubernatis G, et al: Rapid identification of viral infections in liver, heart, and kidney allograft biopsies by in situ hybridization (Letter). Am J Surg Pathol 1989; 13:80-82

226. Debure A, Celton JL, Cartron J, et al: Granulocyte-associated immunoglobulins in renal transplant recipients with cytomegalovirus infection. Lancet 1988; 2:1338-1340

227. Verheyden JP: Evolution of therapy for cytomegalovirus infection. Rev Infect Dis 1988; 10(suppl 3):477-489

228. Cantarovich M, Hiesse C, Lantz O, et al: Treatment of cytomegalovirus infections in renal transplant recipients with 9-(1,3-dihydroxy-2-propoxymethyl)-guanine. Transplantation 1988; 45:1139-1141

229. Stoffel M, Gianello P, Squifflet JP, et al: Effect of 9-(2-hydroxy-1-[hydroxymethyl] ethoxymethyl) guanine (DHPG) on cytomegalovirus pneumonitis after renal transplantation. Transplantation 1988; 46:594-595

230. Snydman DR: Ganciclovir therapy for cytomegalovirus disease associated with renal transplants. Rev Infect Dis 1988; 10(suppl 3):554-562

231. Ringdén O, Lönnqvist B, Paulin T, et al: Pharmacokinetics, safety and preliminary clinical experiences using foscarnet in the treatment of cytomegalovirus infections in bone marrow and renal transplant recipients. J Antimicrob Chemother 1986; 17:373-387

232. Aulitzky WE, Tilg H, Niederwieser D, et al: Ganciclovir and hyperimmunoglobulin for treating cytomegalovirus infection in bone marrow transplant recipients (Letter). J Infect Dis 1988; 158:488-489

233. Goodman JL: Possible transmission of herpes simplex virus by organ transplantation. Transplantation 1989; 47:609-613

234. Griffin PJA, Colbert JW, Williamson EPM, et al: Oral acyclovir prophylaxis of herpes infections in renal transplant recipients. Transplant Proc 1985; 17:84-85

235. Rubin RH, Jenkins RL, Shaw BW, et al: The acquired immunodeficiency syndrome and transplantation. Transplantation 1987; 44:1-4

236. Dummer JS, Erb S, Breinig MK, et al: Infection with human immunodeficiency virus in the Pittsburgh transplant population—A study of 583 donors and 1043 recipients, 1981-1986. Transplantation 1989; 47:134-139

237. Kumar P, Pearson JE, Martin DH, et al: Transmission of human immunodeficiency virus by transplantation of a renal allograft, with development of the acquired immunodeficiency syndrome. Ann Intern Med 1987; 106:244-245

238. Carbone LG, Cohen DJ, Hardy MA, et al: Determination of acquired immunodeficiency syndrome (AIDS) after renal transplantation. Am J Kidney Dis 1988; 11:387-392

239. Rubin H, Tolkoff-Rubin NE: The problem of human immunodeficiency virus (HIV) infection and transplantation. Transplant Int 1988; 1:36-42

240. Schwarz A, Hoffmann F, L'age-Stehr J, et al: Human immunodeficiency virus transmission by organ donation—Outcome in cornea and kidney recipients. Transplantation 1987; 44:21-24

241. Oliveira DB, Winearls CG, Cohen J, et al: Brief communications: Severe immunosuppression in a renal transplant recipient with HTLV-III antibodies. Transplantation 1986; 41:260-263

242. Sheil AG: Cancer after transplantation. World J Surg 1986; 10:389-396

243. Penn I: Transmission of cancer with donor organs. Transplant Proc 1988; 20:739-740

244. Sheil AGR, Flavel S, Disney APS, et al: Cancer development in patients progressing to dialysis and renal transplantation. Transplant Proc 1985; 17:1685-1689

245. Sheil AGR, Flavel S, Disney APS, et al: Cancer incidence in renal transplant patients treated with azathioprine or cyclosporin. Transplant Proc 1987; 19:2214-2216

246. McLelland J, Chu AC: Skin tumours in renal allograft recipients. J R Soc Med 1989; 92:110-111

247. Hanto DW, Frizzera G, Gajl-Peczalska KJ, et al: Epstein-Barr virus, immunodeficiency and B-cell lymphoproliferation. Transplantation 1985; 39:461-472

248. Ho M, Miller G, Atchison RW, et al: Epstein-Barr virus infections and DNA hybridization studies in posttransplantation lymphoma and lymphoproliferative lesions: The role of primary infection. J Infect Dis 1985; 152:876-886

249. Nalesnik MA, Jaffe R, Starzl TE, et al: The pathology of posttransplant lymphoproliferative disorders occurring in the setting of cyclosporine A-prednisone immunosuppression. Am J Pathol 1988; 133:173-192

250. Toussaint C, Kinnaert P, Vereerstraeten P: Late mortality and morbidity five to eighteen years after kidney transplantation. Transplantation 1988; 45:554-558

251. Rao KV, Andersen RC: Long-term results and complications in renal transplant recipients—Observations in the second decade. Transplantation 1988; 45:45-52

252. Rao KV, Kasiske BL, Bloom PM: Acute graft rejection in the late survivors of renal transplantation—Clinical and histological observations in the second decade. Transplantation 1989; 47:290-292

253. Sibley RV, Snover DC: The use and interpretation of biopsies in the management of the post-transplant patient, chap 26, *In* Cerilli GJ, (Ed): Organ Transplantation and Replacement. Philadelphia, JB Lippincott, 1988, pp 394-422

254. Oguma S, Banner B, Zerhe T, et al: Participation of dendritic cells in vascular lesions of chronic rejection of human allografts. Lancet 1988; 2:933-936

255. Foster MC, Wanham PW, Rowe PA, et al: The late results of renal transplantation and the importance of chronic rejection as a cause of graft loss. Ann R Coll Surg Engl 1989; 71:44-71

256. Rovelli M, Palmeri D, Vossler E, et al: Noncompliance in organ transplant recipients. Transplant Proc 1989; 21(pt 1):833-841

257. Didlake RH, Dreyfus K, Kerman RH, et al: Patient noncompliance: A major cause of late graft failure in cyclosporine-treated renal transplants. Transplant Proc 1988; 20(suppl 3):63-69

258. Fine RN: The adolescent with end-stage renal disease. Am J Kidney Dis 1985; 6:81-85

259. Reznik VM, Jones KL, Durham BL, et al: Changes in facial appearance during cyclosporin treatment. Lancet 1987; 1:1405-1407

260. Stewart RS: Psychiatric issues in renal dialysis and transplantation. Hosp Community Psychiatry 1983; 34:623-681

261. Korbet SM, Schwartz MM, Lewis EJ: Recurrent nephrotic syndrome in renal allografts. Am J Kidney Dis 1988; 11:270-276

262. Berger J: Recurrence of IgA nephropathy in renal allografts. Am J Kidney Dis 1988; 12:371-372

263. Mathew TH: Recurrence of disease following renal transplantation. Am J Kidney Dis 1988; 12:85-96

264. Brensilver JM, Mallat S, Scholes J, et al: Recurrent IgA nephropathy in living-related donor transplantation: Recurrence or transmission of a familial disease? Am J Kidney Dis 1988; 12:147-151

265. Vincenti F, Biava C, Tomlanovitch S, et al: Inability of cyclosporine to completely prevent the recurrence of focal glomerulosclerosis after kidney transplantation. Transplantation 1989; 47:595-598

# High-Dose Epinephrine Therapy and Other Advances in Treating Cardiac Arrest

*Discussant*
MICHAEL L. CALLAHAM, MD

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.*

RICHARD K. ROOT, MD*: *Dr Michael Callaham, chief of our division of Emergency Medicine since 1982 and also a Professor of Medicine, will discuss a subject pertinent to anyone who works in emergency services: advances in the management of cardiac arrest.*

MICHAEL L. CALLAHAM, MD†: The topic of the management of cardiac arrest is very broad, so in this review I will focus on a few areas in which there have been the most controversy and change.

## Are the Advanced Cardiac Life Support Guidelines a Standard of Care?

A word of warning. Many of my conclusions are not in agreement with what is taught in the American Heart Association's Advanced Cardiac Life Support (ACLS) course. If a physician is involved in treating a cardiac arrest perhaps once a year or less often, then the best choice would be to take the ACLS course, memorize the algorithms, and think no more about it. If, on the other hand, a physician is involved in resuscitation more frequently, he or she has an obligation to read the literature, to be informed, and to deviate intelligently from standard protocols. Everybody worries that this is illegal or that they are violating a standard of care and that they could be sued, for example, for giving larger doses of epinephrine than are recommended. To alleviate these fears, I would remind them of a crucial disclaimer in the article on the Standards and Guidelines for Advanced Cardiac Life Support published in the *Journal of the American Medical Association.*[1] It states that the ACLS standards and guidelines are not intended to imply that justifiable deviations by qualified physicians represent a breech of the medical standards of care or that new knowledge, new techniques, or clinical experience are not valid reasons for alternative approaches. It is written there in black and white that physicians are justified in deviating from the guidelines if they do so on the basis of knowledge or expertise.

Although I am going to discuss the use of catecholamines and bicarbonate, these drugs are not the most important priorities in resuscitation, and they never will be. Only a small minority of patients will ever be saved by them. The only type of cardiac arrest treated effectively is ventricular fibrillation, and the treatment of ventricular fibrillation is prompt defibrillation, not medication use.

## Catecholamine Use in Cardiac Arrest

Epinephrine has been in standard use for resuscitating patients with cardiac arrest for 30 to 40 years. Let me review how adrenergic drugs work in cardiac arrest. What physicians try to achieve with chest compression and drug administration is an adequate coronary artery perfusion pressure. Coronary artery perfusion pressure, which equals the aortic diastolic pressure minus the right atrial diastolic pressure, determines blood flow through the heart. Studies in animals show that a minimal coronary artery perfusion pressure of about 20 mm of mercury is needed to resuscitate the heart.[2]

Typical early experiments done in 1965 by Joseph Redding, one of the pioneers of cardiac arrest research, showed that if dogs in cardiac arrest received basic cardiopulmonary resuscitation (CPR) only, about 30% of them were resuscitated.[3] These animals had an aortic diastolic pressure of less than 20 mm of mercury, so obviously the coronary artery perfusion pressure could not have been good. When given epinephrine, the diastolic pressure rose to over 30 mm of mercury, and 100% of animals were resuscitated. When given isoproterenol, primarily a $\beta$-adrenergic agent, the diastolic pressure fell, and the resuscitation rates were lower than when no drugs were given at all. When methoxamine, a pure $\alpha$-adrenergic agent, was given, the diastolic pressure rose even further, and 100% were resuscitated. These and other studies showed that essentially all the benefits of adrenergic drugs in cardiac arrest are derived from the $\alpha$-adrenergic effects.[4] The $\beta$-adrenergic effects are not crucial to resuscitation insofar as is known and have no effect on defibrillation. $\alpha$-Adrenergic receptor stimulation causes vasoconstriction throughout the vascular bed, raises the perfusion pressure, and shunts blood to the heart and brain, allowing resuscitation.

*Professor and Chair, Department of Medicine, University of California, San Francisco (UCSF), School of Medicine.

†Chief of Division of Emergency Medicine, Professor of Medicine, UCSF School of Medicine.

(Callaham ML: High-dose epinephrine therapy and other advances in treating cardiac arrest [Medical Staff Conference]. West J Med 1990 Jun; 152:697-703)

ABBREVIATIONS USED IN TEXT

ACLS = Advanced Cardiac Life Support
ATP = adenosine triphosphate
CPR = cardiopulmonary resuscitation
UCSF = University of California, San Francisco

Studies in animals have proved that epinephrine is effective—there have been no studies in humans—but what is the proper dose? The American Heart Association has always recommended giving 0.5 to 1.0 mg of epinephrine every five minutes. Based on weight, that is equivalent to 7.5 to 17 μg per kg every five minutes. On what basis did they choose this dose? In the first studies conducted by Crile and Dolley in 1906, they used 1 to 2 mg intravenously in a 20-kg dog, which averages 200 μg per kg.[5] Redding, who did much of the research on which the original ACLS guidelines were based, used doses of 75 to 150 μg per kg. Particularly interesting is a paper he published in 1965 in which he picked a dose that he was sure would be ineffective, which he refers to repeatedly as "suboptimal."[6] That dose was 10 to 20 μg per kg, essentially the dose that the ACLS guidelines recommend be used in humans. This dose had no effect at all.

Nonetheless, the standard low ACLS-recommended dose has been unchanged up until the present time, although it has never been shown to be effective in any species. In recent years more sophisticated studies of the effects of epinephrine on regional blood flow through various portions of the heart measured by radioactive microspheres found that administering 20 μg per kg of epinephrine did not provide sufficient blood flow for resuscitation (Figure 1).[7] In a series of elegant studies, Brown and co-workers showed that a dose of 200 μg per kg is needed to provide significant blood flow (Figure 2).[8] Similar results have been shown for cerebral artery blood flow.

In the past few years, these results in animals have begun to be substantiated in humans. Humans in whom standard ACLS therapy failed were given graded doses of epinephrine. The diastolic pressure rose only slightly when 1 mg of epinephrine was administered but rose more sharply with doses as high as 5 mg given intravenously.[9] This is a relatively small dose in humans; 15 mg of epinephrine would be needed for a dose of 200 μg per kg. A similar study in which patients were given 200 μg per kg of epinephrine showed an average increase of 12 mm of mercury in coronary artery perfusion pressure. Some persons increased their diastolic pressure by 45 mm of mercury.[10] Recently a case was reported of a patient who had been in refractory ventricular fibrillation for 22 minutes, was given 5 mg of epinephrine, was resuscitated, and eventually was sent home neurologically intact—not the usual outcome for such a long cardiac arrest.[11] A second report described a patient with asystole for 36 minutes; the patient received 6 mg of epinephrine and was resuscitated to a sinus tachycardia and brief normotension. Seven children in arrest were treated with 200 μg per kg after standard therapy failed; six had a prompt return of spontaneous circulation, and four were long-term survivors.[12]

We have had extensive experience with these large doses over the past few years. For example, in 49 adults we treated with epinephrine in cardiac arrest, 29 (59%) of those given high doses had a return of circulation compared with 7 (14%) of those given standard ACLS doses.[13] High-dose epinephrine was given to these patients late in arrest in a nonrandomized fashion, however, and did not enhance ultimate survival.

Could epinephrine use be doing harm in this situation? Certainly 15-mg doses bring this concern to mind. Similarly, large doses injected into somebody with a perfusing rhythm could well be lethal. High levels of β-adrenergic stimulation can cause direct myofibrillar destruction and also might increase the heart rate and blood pressure after resuscitation, increasing the risk of ischemia. High doses of epinephrine can cause arrhythmias, acidosis—the drug itself is acidotic—and pulmonary edema. These adverse effects, however, have been reported chiefly in cases of overdose not involving cardiac arrest.

We have closely examined 63 of our patients who survived longer than six hours after resuscitation from cardiac arrest.[14] Half received standard doses and half received high

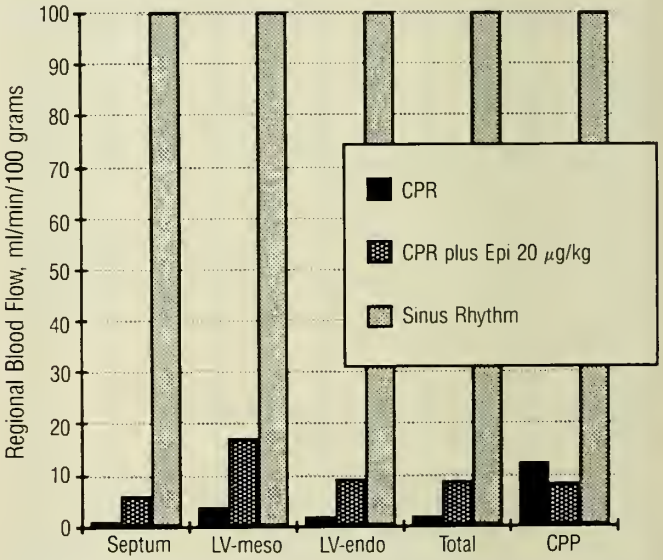



**Figure 1.**—The effects of standard epinephrine doses are shown on regional blood flow. Regional blood flow achieved by standard advanced cardiac life support doses of epinephrine (20 μg/kg) is insufficient to achieve the 25 ml per minute per 100 grams needed for resuscitation (from Brown et al[7]). CPP = coronary [artery] perfusion pressure, CPR = cardiopulmonary resuscitation only, CPR plus Epi 20 μg/kg = CPR plus epinephrine at that dose, LV-endo = left ventricular endocardium, LV-meso = left ventricular mesocardium

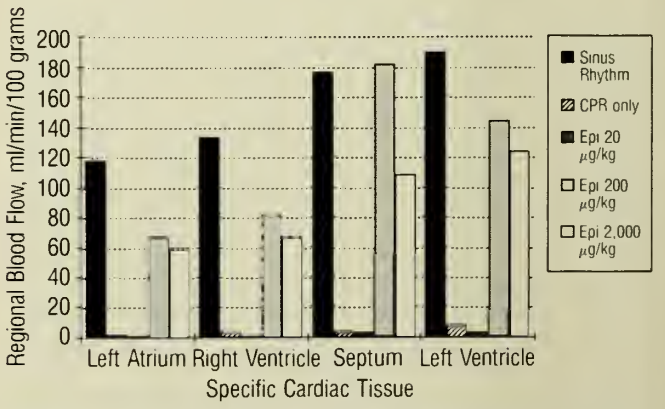



**Figure 2.**—The effects of graded doses of epinephrine on regional blood flow are shown. Doses of epinephrine of 200 μg/kg are needed to achieve the blood flow threshold of 25 ml/minute/100 grams needed to resuscitate the heart; the standard advanced cardiac life support doses of 20 μg/kg are inadequate. Doses of 2,000 μg/kg do not further improve blood flow (from Brown et al[8]). CPR = cardiopulmonary resuscitation, Epi = epinephrine

doses; our record dose (in a neurologically intact survivor) so far is 105 mg. We looked carefully for every conceivable complication of epinephrine use—electrolyte abnormalities, arrhythmias, postresuscitation hypertension, evidence of myocardial infarction, pulmonary insufficiency, elevated creatine kinase levels and MB isoenzyme fractions, and the like. We found no significant differences in the frequency or severity of any of these complications in the high-dose and low-dose groups, so we feel comfortable that even high doses of epinephrine can be given safely. Adverse effects would have to be great indeed to be worse than the certain death that these patients otherwise face, but our experience shows that adverse effects are almost nonexistent.

We use a 30-mg vial of a 1:1,000 solution of epinephrine (Bristojects are impractical for these doses), and we give 200 μg per kg (15 mg for a 70-kg person) by intravenous push every five minutes. We do not worry about the total dose as long as the patient remains in cardiac arrest. We do not use intravenous drips because they are too slow and unpredictable in the amount they deliver. As soon as there is a return of the circulation, the epinephrine is switched to dopamine if, as is often the case, the patient is hypotensive.

Could other adrenergic drugs be better than epinephrine in cardiac arrest? I have already mentioned the successful use of methoxamine, an α-adrenergic agonist. β-Adrenergic drugs buffer intracellular pH changes, but everything else they do during cardiac arrest is undesirable. They cause vasodilation and a lower perfusion pressure and increase the vigor of fibrillation, increasing the cardiac energy consumption and decreasing coronary artery perfusion. Early studies in 1965 showed that administering isoproterenol hydrochloride lowered the diastolic pressure and decreased the likelihood of resuscitation. Like other important findings, this was ignored in the ACLS recommendations. Subsequent studies showed that isoproterenol causes diffuse vasodilation, increasing cardiac output at the expense of the heart and the brain. Coronary artery flow is worse after isoproterenol administration than it is after no treatment at all (Figure 3),[15] but it was not deleted from the ACLS protocols until the 1985 revision.

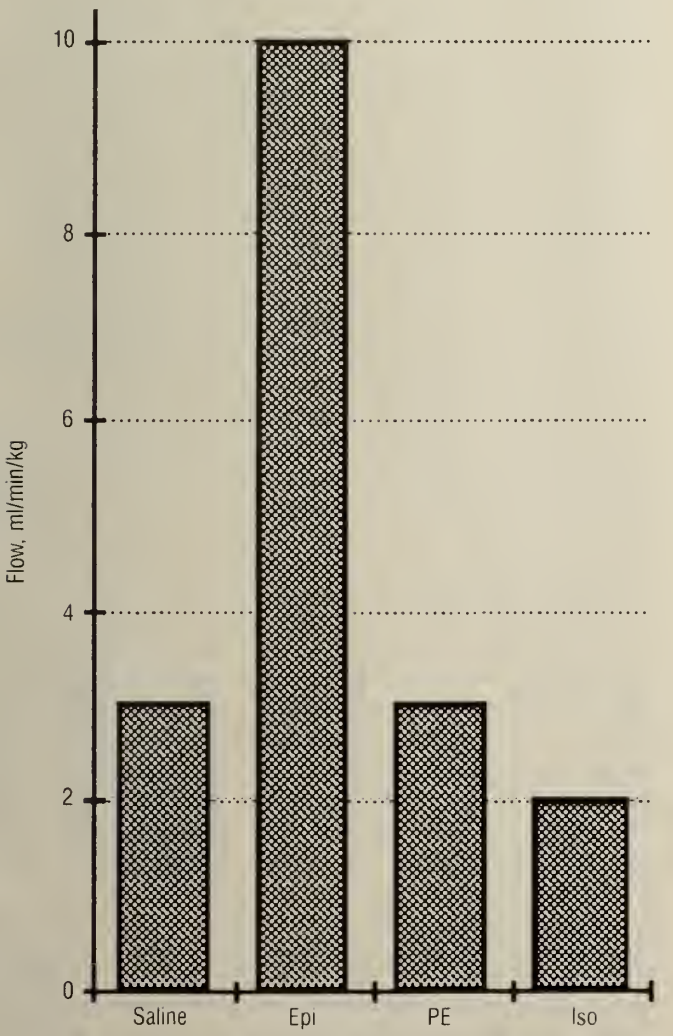



**Figure 3.**—The effects of various adrenergic drugs are shown on coronary artery blood flow during cardiac arrest (from Holmes et al[15]). Epi = epinephrine, Iso = isoproterenol hydrochloride, PE = phenylephrine hydrochloride

There is little literature on the use of dopamine. In dogs, both epinephrine and dopamine use produced a 95% return of the circulation, but the dose of dopamine used was 2,000 μg per kg.[16] Two more recent studies also suggest that in large doses dopamine may have a role in treating cardiac arrest. In one, dopamine at only 15 μg per kg eliminated the benefits (in terms of increased diastolic pressure) seen with incremental doses of epinephrine.[17] The implication is that that dose of dopamine caused maximal vasoconstriction. I find this difficult to believe, and the observation has not been confirmed to date. A study in pigs compared the use of 45 μg per kg of dopamine with that of 45 μg per kg of epinephrine.[18] The resuscitation results were the same, but dopamine produced its effects faster—174 seconds versus 667 seconds to resuscitation—and the animals resuscitated with dopamine were reported to have less hypertension and tachycardia. These are preliminary data, however, and I would not recommend using dopamine in place of epinephrine at this time.

Methoxamine and phenylephrine are theoretically attractive because they are pure α-adrenergic agents. The chief problem with using methoxamine hydrochloride is that its effects last for several hours, and a recent prospective trial in humans showed methoxamine resuscitation and discharge rates 50% lower than those for epinephrine.[19]

Phenylephrine hydrochloride has been shown effective only at very high doses, and it has no proven advantages over epinephrine. Norepinephrine is theoretically attractive because of its strong α-adrenergic and its β-adrenergic activity. In animals the resuscitation rate with norepinephrine was as good as with epinephrine, and resuscitation from ventricular fibrillation arrest was much quicker.[20] This certainly warrants more study, but, as with other catecholamines, there is not yet enough evidence to warrant using it in place of epinephrine in humans.

In summary, epinephrine is effective in high doses, which should be given as early as possible, and it remains the standard catecholamine drug to use in cardiac arrest. The doses recommended in ACLS guidelines have never been shown to have any benefit in any species and probably should be abandoned.

The use of isoproterenol, dobutamine, or low-normal doses of dopamine is contraindicated because their β-adrenergic effects cause vasodilation, decrease the coronary artery perfusion pressure, and worsen the outcome. Methoxamine and phenylephrine, pure α-adrenergic agents, have not lived up to their initial promise.

### Training the Public in CPR

Let us leave pharmacology for a minute. How many physicians caring for high-risk cardiac patients specifically recommend CPR training to family members? Very few, and this reflects one of the failures of the medical community. Layperson bystander CPR is known to work, and yet physicians so often fail to prescribe it. Cardiac arrest most often occurs at home, and the person most likely to witness it is a family member, but these are typically the people least likely to have been trained in CPR. Physicians should always recommend CPR training for the family of high-risk cardiac patients. It can make all the difference; with it, a victim of out-of-hospital ventricular fibrillation has as much as a 50% chance of full functional recovery. Too many physicians have become accustomed to seeing and managing a case of nearly hopeless asystolic arrest and have forgotten that patients can be awake and talking half an hour after an arrest.

### Automatic Defibrillators

One of the biggest advances in the past few years is the automatic defibrillator. It is a self-contained, electronic device that a minimally trained layperson can attach to a patient. The machine analyzes the cardiac rhythm with sophisticated electronic algorithms; if it detects ventricular fibrillation, it administers a shock to the patient. These defibrillators are very accurate. They have great potential because they can be placed in the hands of people who have minimal medical skills but who are often the first to reach the scene of a prehospital cardiac arrest. In San Francisco, we helped train the entire fire department to use these. In our city, the firefighters routinely arrive at a scene of cardiac arrest six to ten minutes sooner than the paramedics. For the first time we are seeing a reversal of San Francisco's low cardiac-arrest save rate, attributed at least partially to our long ambulance response times. We are now seeing a notable number of patients resuscitated in the field and conscious on arrival in the emergency department because of early defibrillation by firefighters.

These machines have several advantages besides the ease and speed with which almost anybody can be trained to use them. First of all, they are the fastest way to defibrillate. With this defibrillator highly trained people will deliver a shock about a minute sooner than with standard equipment. This gain in time, which is very important in ventricular fibrillation, is achieved partly because the semiautomatic device delivers the shock through pads, which are faster than paddles.[21] The device also senses and shocks ventricular fibrillation faster than can be done manually.

In Seattle, 30% of patients whose ventricular fibrillation was treated by firefighters with this defibrillator were discharged from the hospital alive. This compares with a survival of about 17% if firefighters just did traditional basic CPR and waited for paramedics to arrive and defibrillate a patient.

Early defibrillation will save far more lives than any pharmacologic intervention. California law now allows lay people to be trained to use this device. I think we are going to see these machines spreading into large corporate headquarters and public places because most members of corporate boards of directors are usually male, of prime age, and have other risk factors for a myocardial infarction. Automatic defibrillators probably also have a place on hospital "crash" carts, where they could cut precious minutes from the duration of arrest by allowing virtually any hospital personnel to do defibrillation.

### Metabolic and Respiratory Acidosis in Cardiac Arrest

Whether metabolic acidosis in cardiac arrest should be treated is worth discussing. Is metabolic acidosis in this situation bad? Physicians were all taught so in medical school. All physicians can recite the theoretic reasons acidosis could be harmful: it could make defibrillation more difficult; it could prevent catecholamines from working; it could worsen cardiac contractility and conduction; and it could make overall resuscitation less likely. Let us examine the literature and see if any of these beliefs are true.

In experiments in animals, there really is no significant metabolic acidosis for the first 15 minutes of resuscitation, and outcome is largely determined in the first 20 minutes. In a sense, what happens later does not much matter. Similarly, most humans are not acidotic before cardiac arrest, even those in an intensive care unit, and they, too, take about 15 minutes for significant metabolic acidosis to develop. On the other hand, respiratory acidosis in cardiac arrest is common, severe, and develops quickly.

What about the effects of acidosis on the defibrillation threshold? Metabolic acidosis does lower the threshold at which the heart fibrillates, but it does not at all affect the amount of energy required to defibrillate the heart.[22] What about catecholamines? The studies on the effects of acidosis on catecholamines are mostly old, mostly primitive, and none of them focused on events during cardiac arrest. Typical results are that acidosis decreases the pressor response to epinephrine by a third to a half, but the blood pressure still increases significantly. So these studies in animals suggest that the effect is blunted but by no means abolished. Preliminary unpublished studies of human victims of cardiac arrest found no relationship between the venous or arterial pH and the response of the coronary artery perfusion pressure to large doses of epinephrine.[23]

In some ways metabolic acidosis might even be beneficial in cardiac arrest. Acidosis increases oxygen unloading from hemoglobin and substantially increases oxygen delivery to tissues. Some studies of cardioplegic solutions have shown that acidotic solutions preserve the adenosine triphosphate (ATP) energy stores of an arrested heart better than alkalotic solutions do. Redding studied the arterial pH of dogs after five minutes of cardiac arrest. The animals that could not be resuscitated had pHs near normal, whereas those that were resuscitated had pHs of 7.2 or 7.1.[6] Certainly metabolic acidosis did not worsen, and perhaps improved, the outcome in these animals. Similar results are seen in humans. The two factors that do predict increased mortality in humans are a pH greater than 7.55 and plasma osmolality greater than 330 mOsm per liter.[24] Both of these thresholds are easily and routinely exceeded with the administration of sodium bicarbonate.

There is thus no proof that metabolic acidosis needs urgent treatment early in arrest. It does not affect defibrillation energy, and although it may blunt the catechol response, there is nothing to suggest that this cannot be overcome by using large doses of catechols. Acidosis may even protect an ischemic heart against further damage during cardiac arrest and may improve the chance of resuscitation.

Even if acidosis should be treated, is bicarbonate a safe

and effective agent for it? The Henderson-Hasselbalch equation predicts that when sodium bicarbonate is given, the only way hydrogen ion concentration can be reduced is by getting rid of the carbon dioxide that is generated in the process. If carbon dioxide cannot be eliminated, acidosis will not be reversed. Bicarbonate administration always increases the $P_{CO_2}$ 6 to 10 mm of mercury, even in normal healthy humans. In a patient with poor perfusion, such as during cardiac arrest, little blood is perfusing the lung and little carbon dioxide can be blown off. In fact, carbon dioxide exhalation in cardiac arrest is virtually nil, and the mixed venous $P_{CO_2}$ is often over 100 mm of mercury.[25] In this setting, bicarbonate is an ineffective buffer and only increases the already severe respiratory acidosis. Studies in animals have shown that bicarbonate has no buffering effect whatever on myocardial tissue in CPR.[26]

No study of cardiac arrest has been completed that showed any benefit from giving bicarbonate. Like ACLS-recommended doses of epinephrine, bicarbonate is a completely unproved therapy in cardiac arrest. On the other hand, the use of bicarbonate has many harmful effects, and the worst of these is the generation of carbon dioxide (Table 1). Now, the pH that matters in cardiac arrest is not the pH that is measured in the arterial blood; it is the intracellular pH that determines whether the heart can resume function. Bicarbonate does not pass through the cell membranes rapidly, and it takes this ion three to five hours to change the intracellular pH.[27] Intracellular pH is well buffered, and it does not drop dramatically in the first 15 or 20 minutes almost regardless of the degree of metabolic acidosis. But the situation is entirely different with carbon dioxide, which crosses the cell membrane quickly and easily. It immediately causes intracellular acidosis because there is virtually a linear relationship between the intracellular $P_{CO_2}$ and the intracellular pH.

A high intramyocardial $P_{CO_2}$ is closely associated with myocardial dysfunction, and the intramyocardial $P_{CO_2}$ rises steadily after cardiac arrest to phenomenal levels. The intramyocardial $P_{CO_2}$ is 240 mm of mercury at 5 minutes and exceeds 400 mm of mercury at 15 minutes.[27] This correlates well with histologic injury, a decreased myocardial oxygen concentration and pH, and decreased ATP. Isolated heart tissue shows the different effects on functions of an identical pH achieved by metabolic versus respiratory acidosis (Figure 4).[28]

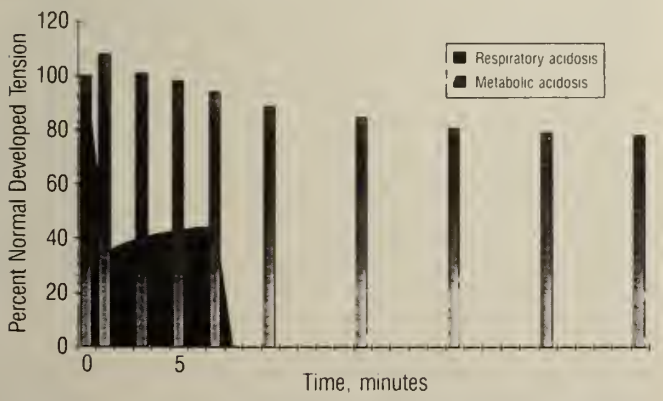



**Figure 4.**—The effect of metabolic versus respiratory acidosis (pH 6.8) is shown on the developed tension of an isolated, perfused, spontaneously beating adult rabbit heart in vitro. Similar results are obtained for effects on cardiac conduction (from Nakanishi et al[28]). Developed tension in metabolic acidosis stabilized after 10 minutes and declined no further for up to an hour. In respiratory acidosis, it stabilized in 5 minutes and persisted at those levels throughout the experiment.

TABLE 1.—*Harmful Effects of Administering Sodium Bicarbonate*

| |
|---|
| Hyperosmolality (solution has osmolality of 2,000 mOsm/liter) |
| Hypernatremia |
| Bohr effect decreases $P_{O_2}$ and oxygen release to tissues |
| Alkalemia causes coronary vasoconstriction |
| Decreases coronary artery perfusion pressure in animals about 50% |
| Elevates $P_{CO_2}$ and causes rapid intracellular acidosis<br>Myocardial $P_{CO_2}$ is highly correlated with ST changes, histologic injury, and decreased ATP and high-energy phosphate levels |
| Depression of cardiac contractility and conduction |
| Increased cardiac oxygen debt and anaerobic metabolism |

ATP=adenosine triphosphate

Recent studies of lactic acidosis in animals show an inverse correlation between mixed venous carbon dioxide and cardiac output; administering sodium bicarbonate increased the mixed venous carbon dioxide levels and directly depressed cardiac function.[29] An elegant study done recently at this medical center showed that even small amounts of bicarbonate given to stable normotensive patients with congestive heart disease lowered $P_{O_2}$ levels, lessened cardiac contractility, worsened myocardial oxygen extraction, increased anaerobic metabolism and myocardial lactate production, and even induced angina and transient pump failure in several patients.[30] Administering a saline solution in equimolar quantities had no such effects.

In conclusion, bicarbonate has many proven harmful effects and no proven beneficial effects in cardiac arrest. The ACLS guidelines have reduced the recommended doses of bicarbonate in every revision. They currently state that bicarbonate should be given on the basis of blood gas values and at the discretion of the team leader, placing the dilemma squarely in the clinician's lap. I personally have not used bicarbonate in cases of cardiac arrest for years. The question that physicians usually ask at this point is, "What if you get the blood gases back and the pH is 6.7; don't you give bicarbonate then?" My answer is still no. Improving ventilation and blowing off carbon dioxide is the answer at this point, for the real problem is severe respiratory acidosis. Unfortunately, acidosis cannot be assessed where it really matters—inside the cell. Typical blood gas values during a well-done resuscitation show an arterial pH of 7.41 and a $P_{CO_2}$ of 19 mm of mercury, and it is tempting to think that the patient is in great shape. But the patient's mixed venous pH is likely 6.5 with a $P_{CO_2}$ of 90 mm of mercury. The moral is that arterial blood gas measurements in patients in cardiac arrest are not useful for much other than determining oxygenation.

## Questions and Answers

PHYSICIAN IN THE AUDIENCE: *Should a patient's age be a factor in whether or not to resuscitate?*

DR CALLAHAM: Resuscitation in the elderly has been fairly well studied, and age alone does not preclude a good outcome. Underlying disease is far more important. Very elderly patients can be successfully resuscitated, and age is not a reason to withhold resuscitation.

PHYSICIAN IN THE AUDIENCE: *Exactly what as a team leader should I tell the pharmacist and the nurse? Should I say,*

*"Open a 30-mg ampule of epinephrine, put it in 250 ml of D5W, and run it in as fast as you can?" How precisely do you give a dose of 200 μg per kg?*

DR CALLAHAM: I do not use epinephrine drips anymore, and the reason is that we want to achieve as high a level of epinephrine as possible as fast as possible for maximal vasoconstriction. Therefore, I use an intravenous push. The other reason I abandoned drips is that "wide open" is a totally unpredictable rate. If you actually measure how much runs in, it may be only 25 to 35 ml over 15 to 20 minutes; it is seldom that the full 250 ml goes in. So we draw up 15 mg from a 30-ml vial of 1:1,000 epinephrine. We usually try to dilute the epinephrine with 10 ml of a saline solution, but that is not based on any studies or hard science. Then we just give it as an intravenous push, assuring high levels very rapidly and making life much simpler for us during the resuscitation.

PHYSICIAN IN THE AUDIENCE: *Is there any reason to use intracardiac epinephrine anymore?*

DR CALLAHAM: No. I wish I had brought along a slide of one of my favorite references from about 20 years ago. I always thought the purpose of the technique was to administer epinephrine directly into the heart and deliver it to the arterial circulation, where it does its work. However, this article stated that the stimulation provided by multiple punctures of the heart with a needle might be sufficient to get it going again. Nobody recommends the intracardiac administration of epinephrine anymore, and postmortem studies have shown that it was seldom accurately delivered to the heart anyhow. The underlying question of whether we might do better if we delivered the epinephrine to the arterial side of the circulation is unstudied and unanswered.

PHYSICIAN IN THE AUDIENCE: *What is the role of calcium?*

DR CALLAHAM: Calcium poses some interesting questions, but I do not have the answers. I thought the use of calcium did not make much sense in the old ACLS protocols. Then a couple of retrospective and somewhat debatable studies were conducted showing that calcium provided no benefit in resuscitation, and it was removed from all of the protocols. I suspect that part of the reason it was removed was the sometimes simplistic logic of physicians. Calcium channel blockers had become available during that period and are regarded as effective, "good" medications. Therefore, the substance they block must be "bad," and we should not administer it. In any event, we do not understand what calcium really does in cardiac arrest. One of the adverse effects of intracellular acidosis is that the hydrogen ion competes with calcium for uptake; calcium administration helps reverse this effect of acidosis.

PHYSICIAN IN THE AUDIENCE: *Has anybody looked at using high-dose epinephrine along with esmolol, a short-acting β-blocker?*

DR CALLAHAM: No, not with a short-acting β-blocker. The only study that examined the two drug types together was done with propranolol, in animals, and β-blockade did not diminish the effectiveness of epinephrine at all. The role of the adrenergic nervous system in cardiac arrest is poorly understood, and there may be some important effect of epinephrine's β-adrenergic properties, but until more studies are done, nobody is going to know.

PHYSICIAN IN THE AUDIENCE: *Are there any data on the use of carbicarb for severe acidosis?*

DR CALLAHAM: Carbicarb is a buffer that consumes rather than generates carbon dioxide, and it has been nicely studied by Dr Bersin of UCSF in an animal model of lactic acidosis, showing that it corrected the pH to nearly normal without elevating the $P_{CO_2}$, without causing intracellular acidosis, and without depressing the heart. That is very attractive, but another study showed it did not buffer the intramyocardial pH in animals during cardiac arrest. The proper question may not be whether we can correct pH in cardiac arrest, other than by eliminating respiratory acidosis, but whether we need to.

PHYSICIAN IN THE AUDIENCE: *What is the availability of carbicarb?*

DR CALLAHAM: It was not available the last I heard. I know it is supposed to come on the market.

PHYSICIAN IN THE AUDIENCE: *Can you tell us whether your work and that of others is beginning to have an effect on the published guidelines regarding the use of bicarbonate? Is it still recommended officially?*

DR CALLAHAM: The recommendations have not changed, but then, of course, the last revision was done in 1985, and the next one is due out in 1990. I suspect, judging by the history of the ACLS Committee, that the next set of recommendations will probably either discard the use of bicarbonate altogether or further decrease its use. Probably they will move part of the way towards a higher dose of epinephrine. Remember that these guidelines are all written by a committee and revisions are only made every five years, so the pace of change is inherently slow and the recommendations are almost by definition out of date. But change does occur.

PHYSICIAN IN THE AUDIENCE: *Would you agree also that the data you showed in this situation would apply to the misuse of bicarbonate in a situation like mesenteric vascular ischemia, where bicarbonate is given as soon as the patient begins to show acidosis by pH measurement alone, disregarding everything else?*

DR CALLAHAM: I am not an authority on the treatment of metabolic acidosis in noncardiac arrest situations, but from my reading of the literature, I do not think there is any situation in which bicarbonate is the buffer of choice for acidosis. We certainly know it does only harm in patients with lactic acidosis. It does not improve the outcome in diabetic ketoacidosis, nor in cardiac arrest, and in fact may well worsen the outcome. Bersin, Chatterjee, and Arieff have shown in elegant studies that even in stable cardiac patients, giving bicarbonate increases the oxygen debt and myocardial anaerobic metabolism, even inducing angina and failure.[30] My guess would be that in five years we will not be using it for this purpose at all.

PHYSICIAN IN THE AUDIENCE: *Considering what you said about the $P_{CO_2}$, it seems that blood gas determinations would be useful to judge the efficacy of ventilation, and maybe that would put the focus on whether you are actually achieving adequate ventilation.*

DR CALLAHAM: No, they are not useful. There are two reasons. One is that there is only poor correlation between arterial and venous blood gas values (or mixed venous blood gas)

in arrest. The other reason is that blood gas values are a measure of both ventilation and perfusion in arrest. The usual situation is that you are ventilating the patient nicely, but you are not perfusing the lungs. Chris Barton and I have been studying end-tidal capnometry here in our emergency department at Moffitt Hospital to measure how much perfusion is actually achieved during CPR. The blood flow through the lungs in most patients is absolutely minimal. This blood flow correlates highly with their end-tidal $Pco_2$ and their coronary artery perfusion pressure, and in turn that value predicts the likelihood of successful resuscitation with a positive predictive value of 91%.[31,32] In most patients in cardiac arrest, the mixed venous carbon dioxide level is high—over 100 mm of mercury—but pulmonary blood flow (and alveolar $Pco_2$) is low. These same patients will often, however, have nearly normal arterial blood gas values, which reflects the trickle of oxygenated blood getting through the pulmonary circuit and not the vast stagnant pool of acidotic, hypercarbic, hypoxic blood in most tissues.

## REFERENCES


1. American Heart Association: Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA 1986; 255:2905-2984

2. Sanders AB, Ewy GA, Taft TV: Prognostic and therapeutic importance of the aortic diastolic pressure in resuscitation from cardiac arrest. Crit Care Med 1984; 12:871-873

3. Pearson JW, Redding JS: Influence of peripheral vascular tone on cardiac resuscitation. Anesth Analg 1965; 44:746-752

4. Otto CW, Yakaitis RW, Blitt CD: Mechanism of action of epinephrine in resuscitation from asphyxial arrest. Crit Care Med 1981; 9:364-365

5. Crile G, Dolley DT: Experimental research into resuscitation of dogs killed by anesthetics and asphyxia. J Exp Med 1906; 8:713-720

6. Redding JS, Pearson JW: Metabolic acidosis: A factor in cardiac resuscitation. South Med J 1967; 60:926-932

7. Brown C, Taylor R, Werman H, et al: Effect of standard doses of epinephrine on myocardial oxygen delivery and utilization during cardiopulmonary resuscitation. Crit Care Med 1988; 16:536-539

8. Brown CG, Werman HA, Davis EA, et al: The effect of graded doses of epinephrine during cardiopulmonary resuscitation on regional myocardial blood flow in a swine model. Circulation 1987; 75:491-497

9. Gonzalez E, Ornato J, Garnett A, et al: Dose-dependent vasopressor response to epinephrine during CPR in human beings. Ann Emerg Med 1989; 18:920-926

10. Paradis N, Martin G, Rivers E, et al: High dose epinephrine in cardiac arrest (Abstr). Crit Care Med 1989; 17:S132

11. Koscove EM, Paradis NA: Successful resuscitation from cardiac arrest using high-dose epinephrine therapy: Report of two cases. JAMA 1988; 295:3031-3034

12. Goetting M, Paradis N: High-dose epinephrine in refractory pediatric cardiac arrest. Crit Care Med 1989; 17:1258-1262

13. Barton C, Callaham ML: High-dose epinephrine significantly improves resuscitation rates in human victims of cardiac arrest (Abstr). Ann Emerg Med 1990; 19:458

14. Callaham ML, Barton C: Potential adverse effects of high-dose epinephrine in human survivors of cardiac arrest (Abstr). Ann Emerg Med 1990; 19:459

15. Holmes HR, Babbs CF, Voorhees WD, et al: Influence of adrenergic drugs upon vital organ perfusion during CPR. Crit Care Med 1980; 8:137-140

16. Otto CW, Yakaitis RW, Redding JS, et al: Comparison of dopamine, dobutamine, and epinephrine in CPR. Crit Care Med 1981; 9:366

17. Gonzalez E, Ornato J, Levine R: Vasopressor effect of epinephrine with and without dopamine during CPR. Drug Intell Clin Pharm 1988; 22:868-871

18. Lindner K, Ahnefeld F, Bowdler I: Comparison of epinephrine and dopamine in CPR (Abstr). Ann Emerg Med 1989; 18:473

19. Olson DW, Thakur R, Stueven HA, et al: Randomized study of epinephrine versus methoxamine in prehospital ventricular fibrillation. Ann Emerg Med 1989; 18:250-253

20. Lindner K, Ahnefeld F: Comparison of epinephrine and norepinephrine in the treatment of asphyxial or fibrillatory cardiac arrest in a porcine model. Crit Care Med 1989; 17:437-441

21. Weaver W, Hill D, Fahrenbruch C, et al: Use of the automatic external defibrillator in the management of out-of-hospital cardiac arrest. N Engl J Med 1988; 319:661-666

22. Yakaitis RW, Thomas JD, Mahaffey JE: Influence of pH and hypoxia on the success of defibrillation. Crit Care Med 1975; 13:139-142

23. Paradis NA, Goetting MG, Rivers EP: Effect of pH on the change in coronary perfusion pressure after epinephrine during CPR in humans (Abstr). Ann Emerg Med 1990; 19:457

24. Weil MH, Ruiz CE, Michaels S, et al: Acid-base determinants of survival after cardiopulmonary resuscitation. Crit Care Med 1985; 13:888-892

25. Weil MH, Grundler W, Yamaguchi M, et al: Arterial blood gases fail to reflect acid-base status during cardiopulmonary resuscitation: A preliminary report. Crit Care Med 1985; 13:884-885

26. Kette F, von Planta M, Weil M, et al: Failure of buffer agents to reverse myocardial acidosis during CPR (Abstr). Circ Clin Res 1988; 36:864A

27. Weil M, von Planta M, Gazmuri R, et al: Incomplete global myocardial ischemia during cardiac arrest and resuscitation. Crit Care Med 1988; 16:997-1001

28. Nakanishi T, Okuda H, Nakazawa M, et al: Effect of acidosis on contractile function in the newborn rabbit heart. Pediatr Res 1985; 19:482-488

29. Bersin RM, Arieff AI: Improved hemodynamic function during hypoxia with carbicarb, a new agent for the management of acidosis. Circulation 1988; 77:227-233

30. Bersin R, Chatterjee K, Arieff A: Metabolic and hemodynamic consequences of sodium bicarbonate administration in patients with heart disease. Am J Med 1989; 87:7-14

31. Barton CW, Callaham ML: Successful prediction by capnometry of resuscitation from cardiac arrest (Abstr). Ann Emerg Med 1988; 17:393

32. Callaham ML, Barton C: Prediction of outcome of cardiac arrest by end-tidal capacity. Crit Care Med 1990; 18:358-362

Epitomes
Important Advances in Clinical Medicine

# Nuclear Medicine

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in nuclear medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in nuclear medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on Nuclear Medicine of the California Medical Association, and the summaries were prepared under its direction.*

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

## Single-Photon-Emission Computed Tomographic Imaging of the Bone

THE PLANAR BONE SCAN is a sensitive test that can show altered bone physiology before it is visible by other radiographic techniques. It is not always possible, however, to determine the cause of abnormal uptake on a scintigram; therefore, specificity is low. This occurs because the images depict metabolic or blood flow alteration in bone that may be due to a variety of conditions. In addition, the planar image represents a two-dimensional summation of all the counts within a three-dimensional field of view. This results in decreased contrast between the lesion and normal tissue and in the "stacking" of bony structures on top of one another.

The application of computed tomography in nuclear medicine has been helpful in overcoming these limitations, whether imaging the skeleton or other organ systems. Instead of imaging along an anatomic plane, data are acquired every 2 to 6 degrees as the camera rotates 180 to 360 degrees around the region of interest. Computer reconstruction produces a three-dimensional image that can be sliced less than 1 cm thick along the transverse, sagittal, or coronal planes. The resulting image contains only the uptake within a particular tomographic plane of interest, thus improving contrast and anatomic localization. Single-photon-emission computed tomographic (SPECT) imaging of the myocardium has improved vessel localization in coronary artery disease, and functional brain imaging has become clinically useful now that the brain can be "sliced" to expose the region(s) of decreased perfusion.

To determine the effectiveness of SPECT over planar imaging in evaluating lower back pain, 100 consecutive patients were studied: 69 abnormalities were detected by planar imaging in 57 patients, and 90 abnormalities were detected by SPECT. None of the abnormalities noted on planar were missed by SPECT, and lesions with low-grade uptake were better visualized by the latter technique.

Compared with plain radiography, SPECT has the added advantage of being able to determine whether an anatomic abnormality is functionally significant. Uptake within a pars interarticularis defect confirms the back pain to be due to spondylolysis or spondylolisthesis noted on plain x-ray films; the absence of uptake suggests another cause.

Single-photon-emission computed tomography enhances the interpretation of bony abnormalities of the skull, hips, and knees. It is almost as sensitive as magnetic resonance imaging in showing internal derangement of the temporomandibular joint and can be particularly useful in showing altered joint mechanics before internal derangement has occurred. Decreased uptake within an area of avascular necrosis of the femoral head may be "hidden" on planar imaging by the overlying acetabulum. Being able to "slice" directly through the femoral head has increased the ability to detect avascular necrosis by as much as 30%. An accurate differentiation can be made between chronic knee pain of meniscal, patellar, or degenerative origin.

Postoperatively, SPECT has been used to assess mandibular graft viability and to distinguish postsurgical changes from pseudarthrosis after spinal fusion. It can be used with any bone-seeking radiopharmaceutical agent, as evidenced by the uptake of neutrophils labeled with gallium 67 or indium 111 in inflammatory bone disease.

The procedure is done easily in most nuclear medicine departments in about 45 minutes with no discomfort to the patient. The relative cost is less than for other specialized imaging studies and is less than half that of magnetic resonance in the imaging of both hips for avascular necrosis.

ANDREW S. KLONECKE, MD
I. ROSS McDOUGALL, MB, ChB, PhD
*Stanford, California*

### REFERENCES

Collier BD, Hellman RS, Krasnow AZ: Bone SPECT. Semin Nucl Med 1987; 17:247-266

Gates G: SPECT imaging of the lumbosacral spine and pelvis. Clin Nucl Med 1988; 13:907-914

Merrick MV: The normal bone scan. *In* Fogelman I (Ed): Bone Scanning in Clinical Practice. Berlin, Springer-Verlag, 1987, pp 19-29

## Single-Photon-Emission Computed Tomography of Cerebral Perfusion

SINGLE-PHOTON-EMISSION computed tomography (SPECT) using cerebral perfusion agent has been added to the list of noninvasive tomographic techniques currently available to evaluate the brain. It is a nuclear imaging method that creates slices of the brain similar in many ways to the images produced by x-ray computed tomography (CT) and magnetic

resonance imaging (MRI). The difference is that brain images obtained with SPECT reflect regional cerebral blood flow rather than brain anatomy as is the case with CT and MRI.

Cerebral perfusion SPECT imaging is closely related to positron emission tomography (PET) in representing a physiologic rather than an anatomic imaging method. The advantage of SPECT is that it uses imaging equipment and radioactive agents that are available in most nuclear medicine laboratories, and the procedure is far less costly than PET. It is comparable in cost to CT imaging and is reimbursable by most insurers.

Cerebral perfusion SPECT imaging is done in a nuclear medicine laboratory following the intravenous injection of either of two radiopharmaceutical agents approved by the Food and Drug Administration: iofetamine hydrochloride I 123 (iodoamphetamine labeled with iodine 123) or hexamethyl-propyleneamine oxime labeled with technetium Tc 99m. Both of these labeled compounds are lipophilic, which permits about 4% to 6% of the agent(s) to concentrate in the brain after passing through the blood-brain barrier. This is provided, of course, that there is sufficient regional blood flow to the territory.

Cerebral perfusion SPECT images depict regional cerebral blood flow as a map showing regional concentrations of radiopharmaceutical uptake in the brain. Uptake (regional cerebral blood flow) is highest in the cortical gray matter, basal ganglia, and cerebellar hemispheres and is normally symmetric and uniform throughout these regions. Single-photon-emission CT images of the brain that show nonuniform or reduced focal uptake suggest that these regions represent areas of decreased regional cerebral blood flow, are otherwise incapable of accumulating the radiopharmaceutical (as with nonviable or infarcted tissue), or both.

One of the principal clinical applications of cerebral perfusion SPECT imaging is in patients with stroke and related cerebrovascular disorders such as transient ischemic attacks, vascular spasm following head trauma or intracerebral bleeding (aneurysm), possible brain death, and the shunting of blood away from cortical regions due to an arteriovenous malformation.

In patients with stroke, it is common to observe areas of decreased perfusion in the ischemic regions. This often precedes the anatomic changes seen on CT or MRI. In many cases, the extent of involvement (decreased perfusion) is greater than that suggested by anatomic imaging. This may be due to the extent of ischemia associated with edema and vascular spasm, which may or may not progress to infarction.

Neurologists are showing increasing interest in using cerebral perfusion imaging to assess possible Alzheimer's disease. The procedure may be helpful in differentiating between the various causes of dementia such as Alzheimer's disease, multiple-infarct dementia, and Pick's disease. Of increasing interest among psychiatrists is the use of cerebral perfusion imaging to assess memory loss found in some cases of clinical depression (pseudodementia). In these cases, cerebral perfusion imaging shows no abnormalities.

The principal scan finding in dementia of the Alzheimer's type is a bilaterally symmetric reduction in uptake in the posterior parietal and temporal regions. Patients with multiple-infarct dementia, however, often show multiple asymmetric zones of reduced perfusion, which may or may not be associated with CT or MRI abnormalities (previous infarcts). By contrast, patients with dementia associated with Pick's disease often show decreased perfusion in the frontal lobes.

Cerebral perfusion imaging also may be done in patients with partial complex seizures to help determine the location and mesial extent (depth) of the site of seizure activity and whether it is single or multifocal. Brain SPECT imaging done immediately following a seizure has been reported to show increased perfusion (uptake) in the area of seizure activity in about 80% of patients. In the interictal period (no seizure activity), uptake may be decreased in the epileptogenic site in as many as 50% of cases.

WILLIAM L. ASHBURN, MD
*San Diego*

REFERENCES

Abdel-Dayem HM, Sadek SA, Kouris K, et al: Changes in cerebral perfusion after acute head injury: Comparison of CT with Tc-99m HM-PAO SPECT. Radiology 1987; 165:221-226

Hill TC, Magistretti PL, Holman BL, et al: Assessment of regional cerebral blood flow (rCBF) in stroke using SPECT and *N*-isopropyl-($^{123}$I)-*p*-iodoamphetamine (IMP). Stroke 1984; 15:40-45

Lee BI, Markand ON, Siddiqui AR, et al: Single photon emission computed tomography (SPECT) brain imaging using N,N,N′-trimethyl-N′-(2 hydroxy-3-methyl-5-$^{123}$I-iodobenzyl)-1,3-propanediamine 2 HCl (HIPDM): Intractable complex seizures. Neurology 1986; 36:1471-1477

Perani D, Di Piero V, Vallar G, et al: Technetium-99m HM-PAO-SPECT study of regional cerebral perfusion in early Alzheimer's disease. J Nucl Med 1988; 29:1507-1514

Roine RO, Launes J, Lindroth L, et al: $^{99m}$Tc-Hexamethylpropyleneamine oxime scans to confirm brain death (Letter). Lancet 1986; 2:1223-1224

## Single-Photon-Emission Computed Tomography of Myocardial Perfusion and the Hepatic Blood Pool

THE RECENT INTRODUCTION of radiopharmaceutical agents that specifically depict organ blood flow has led to an explosion of interest in single-photon-emission computed tomography (SPECT). Major imaging equipment manufacturers indicate that SPECT sales are second in growth only to those of color Doppler ultrasonography.

Although the myocardial distribution of thallium 201 has been the accepted technique for the noninvasive assessment of myocardial blood flow and, hence, coronary artery disease, SPECT has considerably improved the definition of flow abnormalities in exercise, rest, and dipyridamole cardiac studies. Compared with planar imaging, SPECT can more often distinguish perfusion deficits adjacent to diaphragmatic or other extracardiac structures. The left ventricular inferior wall is much more clearly delineated. In addition, the use of the prone decubitus position for imaging has improved the specificity of the detection of inferior wall disease.

The overall sensitivity for detecting substantial coronary artery disease is above 90% with a specificity of about 75% to 80%, which surpasses that of standard treadmill tests. Stress SPECT studies following the administration of thallous chloride Tl 201 are particularly useful in women—who have an unacceptably high rate of false-positive results on standard treadmill testing—and in patients with atypical symptoms or "silent ischemia." Nevertheless, the single most important factor for a good thallium evaluation of myocardial ischemia is an adequate stress test, either using treadmill exercise or by inducing increased coronary artery flow using dipyridamole in patients physically unable to exercise because of musculoskeletal, pulmonary, or peripheral vascular disease.

Another important caveat is that certain disorders of the heart can reduce the specificity for detecting atherosclerotic coronary artery disease. Left bundle branch block may produce a relative perfusion deficit in the interventricular septum in the absence of atherosclerotic disease. Small vessel disease, cardiomyopathy, and infiltrating disease of the myocardium, such as amyloid or sarcoid, can give abnormal thallium uptake in the presence of normal large vessels on angiography.

The three-dimensional evaluation of ischemic heart disease afforded by SPECT lends itself to reproducible, semiquantitative analysis in the form of a "polar map" or "bull's-eye" display of left ventricular perfusion. Individual patient data are compared with a normal data base of $^{201}$Tl myocardial uptakes. Substantial areas of reduced perfusion are described in standard deviations from normal. Such quantitation can reduce interobserver variability, improve localization of specific vascular territories, and perhaps help identify diffuse and subcritical stenoses. Single-photon-emission computed tomography and quantitation can be helpful in determining which stenosis seen on coronary angiography is probably most responsible for a patient's symptoms and may be amenable to angioplasty or bypass.

New radiopharmaceutical agents (yet to be approved by the Food and Drug Administration as of this writing) labeled with technetium Tc 99m (the least expensive and most available radionuclide) promise to improve image quality and, it is hoped, reduce the cost of SPECT cardiac perfusion scans. These new agents are sestamibi (Du Pont) and teboroxime (Squibb).

Technetium Tc 99m-labeled red blood cell imaging using SPECT has enabled diagnosticians to more precisely identify hemangiomas, which are the most common benign neoplasm of the liver, with a 7% incidence at autopsy. The usual scenario is that of a liver lesion detected by computed tomography (CT) or ultrasonography and referred for functional assessment. Single-photon-emission CT is superior to planar imaging for lesion detectability, particularly for smaller masses that are deeply seated in the hepatic parenchyma. Characteristically, a benign hemangioma has a decreased early flow but increased delayed blood pool within the lesion, a pattern not seen in hepatoma or metastatic lesions. Tomographic slices in the transverse, sagittal, and coronal planes can be directly compared with those of CT. Hepatic blood pool scans using SPECT are now part of the routine, noninvasive workup of liver masses of unclear significance.

The tomographic evaluation of normal and abnormal function makes SPECT a powerful tool in the hands of nuclear medicine physicians encountering these common and pertinent problems in disorders of the heart and liver.

DAVID H. LEWIS, MD
WIL B. NELP, MD
*Seattle*

REFERENCES

Brodsky RI, Friedman AC, Maurer AH, et al: Hepatic cavernous hemangioma: Diagnosis with $^{99m}$Tc-labeled red cells and single photon emission CT. AJR 1987; 148:125-129

Cerqueira MD, Harp GD, Ritchie JL: Evaluation of myocardial perfusion and function by single photon emission computed tomography. Semin Nucl Med 1987; 17:200-213

Guze BH, Hawkins RA: Utility of the SPECT Tc-99m labeled RBC blood pool scan in the detection of hepatic hemangiomas. Clin Nucl Med 1989; 14:817-818

Iskandrian AS, Heo J, Askenase A, et al: Thallium imaging with single photon emission computed tomography. Am Heart J 1987; 114:852-865

Seldin DW, Johnson LL, Blood DK, et al. Myocardial perfusion imaging with technetium-99m SQ30217: Comparison with thallium-201 and coronary anatomy. J Nucl Med 1989; 30:312-319

Wackers FJ, Berman DS, Maddahi J, et al: Technetium-99m hexakis 2-methoxyisobutyl isonitrile: Human biodistribution, dosimetry, safety, and preliminary comparison to thallium-201 for myocardial perfusion imaging. J Nucl Med 1989; 30:301-311

## Gastric Emptying Revisited

RADIONUCLIDE GASTRIC EMPTYING studies are being increasingly used to evaluate esophageal and gastric disorders. Barium meals do not reproduce the usual patient feeding and are nonphysiologic, often cover a limited time period, and are relatively nonquantitative. In addition, radiation exposure is usually less with radionuclide gastric emptying studies despite the ability to image continuously or intermittently for hours.

Both liquid (water) and solid (chicken liver, egg, resin, and the like) meals can be used. Radiolabeled chicken liver is difficult to prepare and not palatable to some, and synthetic materials are not readily available, making a labeled egg preparation the best solid meal.

The radioactive labels used are technetium Tc 99m sulfur or albumin colloid and indium In 111 if a second label is desired to have both a radiolabeled solid component and a radiolabeled liquid component within a single meal. A liquid meal alone is usually used for children or in certain disorders and a solid meal alone in adults.

In children, $^{99m}$Tc-colloid in the patient's usual feeding formula more nearly reproduces normal feeding with its usual nutrient and fat content better reflecting its effect on gastric emptying. One-minute images are taken continuously for 60 minutes. Delayed images, when needed, are obtained at 4 and 24 hours. Esophageal reflux, gastric emptying, and pulmonary aspiration are examined visually, and regions of interest are used to quantitatively evaluate gastric emptying at 60 minutes. Geometric correction is not used in adults or in children. Also, a decay correction is not made as this is considered within the normal values. The upper limits of normal for the retained gastric content of a liquid meal at 60 minutes is either 50% or less, or a half-life of 60 minutes.

Although the liquid portion of a meal may empty more rapidly than the solid portion, it is still slower than a liquid meal alone. Symptoms observed in older children and adults are usually related to the solid portion of a meal, and therefore only the solid (egg) portion of a standard meal need be labeled. If the liquid emptying is also desired, it can be done separately. Images of a minute each are taken every 10 minutes for 90 minutes. An image of a region of interest of the stomach is taken. Normal gastric retention at 90 minutes is 55% or less. This value considers the supine position during the study, the anterior-inferior descent of the meal within the stomach, the normal lag time of converting the meal to chyme, and the decay of the $^{99m}$Tc. Decay corrections are never applied to the patient data but are included within the normal values.

GERALD KIRK, MD
*Loma Linda, California*

REFERENCES

Horowitz M, Collins PJ, Shearman DJC: Disorders of gastric emptying in humans and the use of radionuclide techniques. Arch Intern Med 1985; 145:1467-1472

Siegel JA, Perri JL, Vitti RA, et al: The physiological significance of the lag phase of gastric emptying (Abstr). J Nucl Med 1986; 27:903-904

Velchik MG, Reynolds JC, Alavi A: Effect of caloric content on gastric emptying (Abstr). J Nucl Med 1988; 29:751

## Hepatobiliary Excretion Scintigraphy Revisited

To REDUCE THE MORBIDITY AND MORTALITY associated with acute cholecystitis, the diagnosis must be made or excluded in any patient seen because of right upper quadrant abdominal pain occurring suddenly. Ultrasonography is the procedure of choice in diagnosing the presence of gallstones, although a stone lodged in the cystic or common bile duct may often be missed. Furthermore, the presence of cholelithiasis of itself does not imply acute cholecystitis. Cholescintigraphy using technetium Tc 99m iminodiacetic acid is a sensitive and accurate examination for the presence of acute cholecystitis and biliary duct obstruction because in 98% of patients acute cholecystitis is caused by obstruction of the cystic duct.

The principal scintigraphic sign of acute cholecystitis is nonfilling of the gallbladder within an hour in spite of normal hepatic excretion, which has a false-positive rate of as high as 10% to 12% because of chronic cholecystitis, pancreatitis, nonfasting (less than 2 hours), prolonged fasting (greater than 12 hours), the use of total parenteral nutrition, alcoholism, hepatocellular disease, and severe intercurrent illness. It is claimed that the false-positive rate can be reduced by taking delayed views as much as four hours later. One study has shown that not only can the rate of false-positive results be reduced to 2% but the total study time can be reduced to an hour by administering intravenous morphine sulfate (0.04 mg per kg body weight) after 30 to 40 minutes when the gallbladder is not visualized and small bowel activity has excluded common duct obstruction. The sphincter of Oddi contracts and raises the intrabiliary pressure. Administering 2.5 mg of intravenous morphine has been shown to nearly double bile duct pressure (12.7 to 20.0 cm of saline). The maximum effect takes place about five minutes after the injection. It has been postulated that the increase in bile duct pressure may be enough to overcome partial or functional obstruction of the cystic duct and thereby raise the incidence of false-positive results. Nevertheless, it is now generally accepted that morphine-augmented cholescintigraphy is a safe and sensitive means of diagnosing acalculous and calculous cholecystitis.

Cholecystokinin and sincalide (0.02 $\mu$g per kg) can be used to empty viscous bile from the gallbladder as seen in patients with prolonged fasting and total parenteral nutrition. The radiopharmaceutic agent is given 30 minutes after injection during the gallbladder filling phase. This procedure can also be used to contract a visualized gallbladder to test common bile duct patency. In one study common bile duct obstruction was detected in 63 of 65 patients, for a positive predictive value of 97%. The two false-positive results were caused by cholangitis of an undetermined origin. Sonographic evaluation alone, however, has a high false-negative rate of 63%. It is usually wise to exclude by sonography the presence of small biliary stones that could be dislodged into the common duct.

Neonatal hepatitis can be differentiated from biliary atresia by administering phenobarbital, 2.5 mg per kg twice per day for three to seven days, to stimulate biliary secretion before administering 1 mCi (37 megabecquerels [MBq]) of $^{99m}$Tc tracer. Intestinal activity seen within 24 hours in a jaundiced infant is probably due to neonatal hepatitis or prolonged hyperalimentation. A lack of intestinal activity in this time period suggests biliary atresia. The sensitivity for detecting biliary atresia is high, approaching 100% in several series. The specificity has been reported from 47% to 63% without pretreatment with phenobarbital to 63% to 94% with pretreatment.

WALTER H. WILLIAMS, PhD, MD
*Tucson, Arizona*

REFERENCES

Choy D, Shi EC, McLean RG, et al: Cholescintigraphy in acute cholecystitis: Use of intravenous morphine. Radiology 1984; 151:203-207

Kaplun L, Weissmann HS, Rosenblatt RR, et al: The early diagnosis of common bile duct obstruction using cholescintigraphy. JAMA 1985; 254:2431-2434

Majd M, Reba RC, Altman RP: Effect of phenobarbital on $^{99m}$Tc-IDA scintigraphy in the evaluation of neonatal jaundice. Semin Nucl Med 1981; 11:194-204

McAfee JG: Update of radiopharmaceuticals for medical imaging. Radiology 1989; 171:593-601

Murphy PA, Salomon J, Roseman DL: Narcotic anesthetic drugs—Their effects on biliary dynamics. Arch Surg 1980; 115:710-711

## Captopril Renograms for Detecting Renovascular Hypertension

RENOVASCULAR HYPERTENSION occurs in about 1% of people in the general population having hypertension. Those with intermediate risk factors have prevalence rates of about 5%. Rates as high as 31% occur in persons with severe hypertension. Hence, the sensitivity and specificity of any screening test for renovascular hypertension must be greater than 90%. Until now, standard tests have not met these criteria, nor have they been shown to be practical for screening. Because the presence of renal artery stenosis does not necessarily imply the presence of renovascular hypertension, the arteriographic demonstration of renal artery stenosis in a hypertensive person is not equivalent to a diagnosis of the disorder. Furthermore, renal artery stenosis, although frequent and more severe among hypertensive patients, occurs without an associated elevation of blood pressure. The ability to identify renovascular hypertension is important because it is amenable to surgical correction and a subsequent reduction of the blood pressure, leading to a decreased rate of hypertension-related disease and death.

Renovascular hypertension characteristically is dependent on increased renin secretion by the juxtaglomerular apparatus of an underperfused stenotic kidney. Renin acts by increasing the production of angiotension II, both a potent vasoconstrictor and a stimulator of aldosterone secretion by the adrenal cortex, prompting an increased resorption of sodium and water in the distal convoluted tubule. Glomerular filtration is maintained in the affected kidney by the vasoconstrictive action of angiotensin on the efferent arteriole. Captopril, an angiotensin-converting enzyme inhibitor, counteracts this vasoconstrictive effect, causing release of the constricting action on the efferent arteriole and a reduction in glomerular filtration. Because this effect can only be shown in patients with renovascular hypertension and not in those with essential hypertension, captopril is being used in radioisotope renography to document this effect and thus the presence of the renovascular disorder. The radioisotope renogram, as a diagnostic tool for renovascular hypertension, has in the past had a sensitivity and specificity of 80% to 85%, which are not significantly better than those of the rapid-sequence intravenous pyelogram, largely because of renal diseases such as chronic pyelonephritis, obstruction, or parenchymal disease that mimic the findings. Captopril renography has become most useful in distinguishing those

abnormalities that are caused by the renin-angiotensin-aldosterone effects of the disorder from those that are not.

Standard renal function evaluation techniques that use either technetium Tc 99m pentetic acid (DTPA) (excreted by glomerular filtration) or iodohippurate sodium I 131 or I 123 (excreted primarily by tubular secretion) show a delayed transit time through the kidney and therefore a prolonged excretory phase that results from the renin effect of reducing urine flow on the affected side. When captopril is administered before these tests, there is a substantial drop in the glomerular filtration rate. This affects the $^{99m}$Tc-DTPA renogram by dropping the rate of tracer accumulation and the iodohippurate renogram by delaying the transit time (time to peak) and excretion rate half-time owing to the altered dynamics. These changes are not noted in essential hypertension where there is either an increase or no significant change in the glomerular filtration rate. In patients with renovascular hypertension with severely reduced renal function, the magnitude of the change may be reduced, making the test less sensitive. In those with complete renal artery stenosis, although renin production is increased, there is no handling of these radiopharmaceuticals as is to be expected. In nearly complete stenosis, there is also no demonstrable captopril effect, but an iodohippurate study does show the classic retention pattern. In mild stenosis (<50%) there is neither increased renin production nor a captopril effect.

Although large-scale studies using captopril in this manner have not yet been done, the well-defined mechanistic response to angiotensin inhibition should significantly enhance the 80% to 85% sensitivity of standard renograms in identifying renovascular hypertension and differentiating it from essential hypertension and other renal diseases.

JOHN MAX VOGEL, MD
*Sacramento, California*

REFERENCES

Dondi M, Franchi R, Levorato M, et al: Evaluation of hypertensive patients by means of captopril enhanced renal scintigraphy with technetium-99m DTPA. J Nucl Med 1989; 30:615-621

Fine EJ: General concepts and applications of the scintirenogram in hypertensive disease. *In* Blaufox MD (Ed): Evaluation of Renal Function and Disease with Radionuclides—The Upper Urinary Tract. Basel, S. Karger, 1989, pp 198-235

Kremer Hovinga TK, de Jong PE, Piers DA, et al: Diagnostic use of angiotensin converting enzyme inhibitors in radioisotope evaluation of unilateral renal artery stenosis. J Nucl Med 1989; 30:605-614

Sfakianakis GN, Bourgoignie JJ, Jaffe D, et al: Single-dose captopril scintigraphy in the diagnosis of renovascular hypertension. J Nucl Med 1987, 28:1383-1392

## Dacryoscintigraphy Revisited

NASOLACRIMAL DUCT OBSTRUCTION is a frequent cause of epiphora (excess tearing). A diagnostic evaluation is required to rule out other common causes of epiphora such as lower lid horizontal laxity or conjunctival inflammation. A proper diagnosis is essential because the traditional treatment of nasolacrimal duct obstruction is surgical correction. Recently a new technique has been described that uses a balloon catheter—like doing coronary angioplasty—to dilate the nasolacrimal duct. This has stimulated a renewed interest in a physiologic assessment of nasolacrimal duct patency.

Two office procedures may be done to evaluate nasolacrimal duct obstruction: irrigation of the lacrimal system and dye testing. Nasolacrimal duct obstruction may be diagnosed when there is complete obstruction to irrigation of the lacrimal system at the level of the nasolacrimal duct. In many patients with epiphora, however, there is no physiologic drainage of tears through the nasolacrimal duct, but forceful irrigation through the nasolacrimal duct may be accomplished (functional nasolacrimal duct obstruction). Functional nasolacrimal duct obstruction may be diagnosed by placing fluorescein dye in the eye and a cotton swab in the nose to recover the dye. This test has been criticized as unreliable because of problems recovering the dye in the nose of some patients.

The tearing process was first studied with radioisotopes in 1973. A major difference between a radionuclide dacryocystogram and an x-ray contrast dacryocystogram is that the radionuclide study is physiologic and better depicts the natural flow of tears. The study consists of placing a drop of technetium Tc 99m pertechnetate in the conjunctival space and imaging the passage of the labeled tears into the nose. X-ray dacryocystography, on the other hand, requires canalization of the nasolacrimal duct and the administration of contrast using pressure, which can mask the anomaly.

Recently 16 patients were studied before balloon dilatation of the nasolacrimal duct. In each case the dacryoscintigram showed the obstruction. In addition, the site of obstruction along the nasolacrimal path was found and the degree of obstruction was apparent. Dacryoscintigraphy is thus a useful diagnostic test to evaluate patients with epiphora and suspected functional nasolacrimal duct obstruction.

KENNETH P. LYONS, MD
BRUCE BECKER, MD
KENNETH ASHTON, MD
*Long Beach, California*

REFERENCES

Carlton WH, Trueblood JH, Rossomondo RM: Clinical evaluation of microscintigraphy of the lacrimal drainage apparatus. J Nucl Med 1973; 14:89-92

Von Denffer H, Dressler J, Pabst HW: Lacrimal dacryoscintigraphy. Semin Nucl Med 1984, 14:8-15

## Radiolabeled Monoclonal Antibodies for Detecting and Treating Cancer

THE USE OF MONOCLONAL ANTIBODIES offers a new procedure, called immunoscintigraphy, for detecting and treating cancer. The basic concept is to use monoclonal antibodies as a carrier to transport the radionuclide to the tumor sites, using the mechanism of the binding of antibody to the site of antigen. When antibodies are labeled with $\gamma$-ray-emitting radionuclides, such as technetium Tc 99m and others, they can be used to detect primary and metastatic lesions. The antibodies can also be labeled with $\beta$-ray-emitting radionuclides such as iodine 131 and others and be applied for treatment.

Radioimmunoscintigraphy is successfully used to detect solid tumors including melanoma; hepatocellular carcinoma, neuroblastoma; carcinomas of the breast, prostate, colorectum, lung, and ovary; and nonsolid tumors such as B-cell and T-cell lymphomas. In our experience, $^{99m}$Tc-anti-melanoma antibody provides excellent quality diagnostic imaging with a high tumor-to-soft-tissue ratio. Besides the known lesions that have been identified, there are many unexpected lesions detected with this radiolabeled antibody and later confirmed to be metastatic melanoma lesions. Because of the need to alter treatment plans, the clinical importance of detecting unexpected sites cannot be overemphasized. This melanoma antibody is currently under the review of the Food and Drug Administration and is expected to be approved this year. Other antibodies such as those of lymphoma, breast cancer, lung cancer, colorectal, and prostate cancer are in the

early stages of investigation and available only in major medical centers.

The treatment of hepatocellular carcinoma, melanoma, neuroblastoma, B-cell and T-cell lymphomas, and ovarian carcinoma has been tried with varied but encouraging results. In one study about 50% of 105 patients with hepatocellular carcinoma responded to the treatment of $^{131}$I-antiferritin antibody. Large doses (more than 200 mCi [7,400 MBq]) of $^{131}$I-Lym-1 or anti-pan-B cell antibody were used to treat B-cell lymphoma with good responses in more than 30 patients.

The possible advantages of using monoclonal antibodies to detect and treat cancer are a binding of tumor-specific monoclonal antibody to the tumor site, providing high-intensity target to background images for tumor detection; a single imaging procedure and a single radiation exposure providing the information of disease in the whole body and eliminating the need for many procedures to stage the cancer; and giving a high radiation dose to tumor while sparing the normal tissue in the radioimmunotherapy.

There are several disadvantages in that only a small amount of injected labeled monoclonal antibody accumulates in the tumor. There is some nonspecific organ binding that varies with different antibodies and labeling methods. Also, all have a short shelf-life, which requires a fresh preparation.

Immunoscintigraphy and radioimmunotherapy may become an essential part of cancer staging and therapy for tumors such as melanoma, lymphoma, and carcinomas of the lung, breast, colon, and prostate.

DAVID C.P. CHEN, MD
MICHAEL E. SIEGEL, MD
*Los Angeles*

REFERENCES

Larson SM: Lymphoma, melanoma, colon cancer: Diagnosis and treatment with radiolabeled monoclonal antibodies. Radiology 1987; 165:297-304

Order SE, Stillwagon GB, Klein JL, et al: Iodine-131 antiferritin, a new treatment modality in hepatoma: A radiation therapy oncology group study. J Clin Oncol 1985; 3:1573-1582

Salk D, Multicenter Study Group: Technetium-labeled monoclonal antibodies for imaging metastatic melanoma: Results of a multicenter clinical study. Semin Oncol 1988; 15:608-618

## Treatment of Bone Metastases

SKELETAL METASTASES are associated with a variety of cancers, being present in more than half of patients having breast or prostate cancer. These metastatic lesions can be extremely painful despite conventional forms of therapy such as chemotherapy, surgical excision, hormonal manipulation, or localized radiation therapy. The use of radionuclides in the treatment of bone metastases has been limited to that of phosphorus 32. Its use has not been widespread, however, owing to substantial hematologic side effects in patients receiving $^{32}$P therapy.

Recently, patients with widespread skeletal metastases have been treated with strontium 89, rhenium 186, and samarium 153. These radionuclides are all $\beta$-ray emitters, with $^{186}$Re and $^{153}$Sm having the additional advantage of $\gamma$-ray emissions that also allow for imaging.

Because the largest clinical experience in Europe and the United States has been with the use of $^{89}$Sr in the treatment of bone metastases, this radionuclide will be discussed in detail.

Strontium 89 is a pure $\beta$-ray emitter with the maximum energy of 1.5 MeV and an effective range in tissue of 0.8 cm. It has a half-life of 50.5 days and is produced by cyclotron. It is available as an aqueous solution of strontium Sr 89 chloride for intravenous injection. Strontium 89 was reported to be effective in relieving bone pain due to metastatic prostate cancer in 80% of patients and 89% of the patients having skeletal metastases due to breast cancer. This was achieved using a dose of 40 $\mu$Ci (1.5 MBq) per kilogram given as a single intravenous injection. Pain relief lasted as long as six months after treatment, and retreatment at three-month intervals was possible without notable hematologic depression.

Because of the relative sparing of bone marrow by $^{89}$Sr-chloride, which is a calcium analogue and not taken up directly by the bone marrow, about 20% of patients in one study showed no significant change in their leukocyte or total platelet count. The remaining 80% of the patients had an average 15% to 20% decrease in total platelets and leukocyte counts by the fifth week after $^{89}$Sr-chloride was administered. A reduction in bone pain did not usually occur until 10 to 14 days after therapy, although a small percentage of patients did experience a flare phenomenon, with a significant increase in pain within 36 to 48 hours after $^{89}$Sr therapy. Repeating the treatment is possible and well tolerated.

Although compounds containing $^{89}$Sr, $^{186}$Re, and $^{153}$Sm are currently available only under investigational new drug protocols, they may be approved by the Food and Drug Administration for routine use in the near future. The use of all of the above radiopharmaceutical agents appears to have significant advantages over that of $^{32}$P in the treatment of skeletal metastases, although a cure of the metastatic skeletal involvement is not possible with current dosage. Considerable palliation of pain and a better quality of life are attainable by using these therapeutic agents.

ROBERT F. CARRETTA, MD
*Fair Oaks, California*

REFERENCES

Blake GM, Zivanovic MA, McEwan AJ, et al: Sr-89 therapy: Strontium kinetics in disseminated carcinoma of the prostate. Eur J Nucl Med 1986; 12:447-454

Maxon HR, Deutsch EA, Thomas SR, et al: Re-186(Sn) HEDP for treatment of multiple metastatic foci in bone: Human biodistribution and dosimetric studies. Radiology 1988; 166:501-507

Robinson RG, Spicer JA, Preston DF, et al: Treatment of metastatic bone pain with strontium-89. Nucl Med Biol 1987; 14:219-222

Singh A, Holmes RA, Farhangi M, et al: Human pharmacokinetics of samarium-153 EDTMP in metastatic cancer. J Nucl Med 1989; 30:1814-1818

## Radionuclide Synovectomy for Chronic Joint Effusion

THE USE OF INTRA-ARTICULARLY ADMINISTERED radiocolloid to selectively eradicate inflamed synovium was pioneered in Europe. Rather than actually surgically removing the synovium, the eventual desired outcome with this treatment is sclerosis of the synovium. Although encouraging results were initially reported in the 1960s using gold Au 198 colloid, this particular tracer had two potential drawbacks: the $^{198}$Au had a $\gamma$-ray emission that added to the radiation exposure with little therapeutic value, and the particle size (0.02 $\mu$m) is small, yielding unacceptable leakage from the joint. More recently, radionuclides that do not emit $\gamma$-rays and are pure $\beta$-ray emitters have been used. The two most common are chromic phosphate P 32 and dysprosium 165 macroaggregates, which also have significantly larger particle size, thus minimizing leakage (approximately 750 $\mu$m and 5 $\mu$m, respectively).

The treatment is a simple outpatient procedure using an

18-gauge needle to do an arthrocentesis and instill the therapeutic dose, usually about 1 mCi (37 MBq) for the bone and 0.5 mCi (18.5 MBq) for an elbow. Simultaneous contrast fluoroscopy or instillation of a small dose of technetium Tc 99m sulfur colloid may be helpful to confirm the location of the needle.

Using $^{32}$P-colloid or $^{165}$Dy-macroaggregates for a year or more has been reported to minimize joint inflammation and effusions in 80% to 85% of patients with rheumatoid arthritis.

Chronic synovitis is a common and significant complication of hemarthrosis in patients with hemophilia. Using intra-articular $^{32}$P-chromic phosphate, we have treated the knees or elbows of 25 patients with a substantial and protracted decrease in the incidence of recurrent hemarthrosis and effusion in approximately 70%.

Radiation synovectomy appears to be a viable and certainly less costly alternative to surgical synovectomy in patients disabled by chronic, large joint effusions that have proved resistant to conventional management.

MICHAEL E. SIEGEL, MD
*Los Angeles*

REFERENCES

Harbert JC: Radiocolloid therapy in joint disease. *In* JC Harbert (Ed): Nuclear Medicine Therapy. New York, Thieme Medical Publishers, 1987, pp 169-186

Sledge CB, Atcher RW, Shortkroff MS, et al: Intra-articular radiation synovectomy. Clin Orthop 1984; 182:37-40

## ADVISORY PANEL TO THE SECTION ON NUCLEAR MEDICINE

DAVID C. PRICE, MD
*Advisory Panel Chair*
*CMA Scientific Board Representative*
*University of California, San Francisco*

LARRY D. GREENFIELD, MD
*CMA Section Chair*
*Fullerton*

JOHN H. MILLER, MD
*CMA Section Secretary*
*Los Angeles*

PATRICK V. FORD, MD
*CMA Section Assistant Secretary*
*Sacramento*

ROBERT F. CARRETTA, MD
*Immediate Past Panel Chair*
*Fair Oaks*

JOSEP G. LLAURADO, MD
*Section Editor*
*Loma Linda University*

I. ROSS MCDOUGALL, MB, ChB, PhD
*Stanford University*

JOHN VOGEL, MD
*University of California, Davis*

KENNETH LYONS, MD
*University of California, Irvine*

RANDALL A. HAWKINS, MD
*University of California, Los Angeles*

WILLIAM L. ASHBURN, MD
*University of California, San Diego*

MICHAEL E. SIEGEL, MD
*University of Southern California*

RICHARD W. MYERS, MD
*Sacramento*

DAVID L. LILIEN, MD
*Newport Beach*

ROBERT J. LULL, MD
*San Francisco*

# Editorials

## Medicine in Extraordinary Times

We live in a period of unprecedented transition both in medicine and in society. There is awesome political upheaval or potential upheaval in many parts of the world. And overshadowing everything everywhere is the destructive threat of nuclear power, were it ever to fall into irresponsible hands. And there are many other risks to human health that also result from progress and achievement in modern science and technology. Even biomedical science in its own way seems to be creating problems in health and health care rather than giving the answers that many hoped and expected it would. These are surely extraordinary times. There are risks, but there are also opportunities for the imaginative and innovative who would take risks.

In many ways medicine and health care are an underlying cause of much that now requires transition and social change, at least in America. For example, more infants and children are living to grow up, and after they grow up, they are living longer. The costs of child care and care of the aged are rising, and the resources for this care are inadequate. Industrial pollutants of land, water, and air are beginning to affect health in innumerable ways and are requiring costly social change to prevent the ill effects that physicians are seeing in their offices. Human behaviors, both normal and in aberration, are having profound effects on the larger society and on health and the costs of health care. New interactions and new interdependencies are developing among physicians, the health care enterprise, and the larger society. All of this is transforming patient care, the health care system, and societal expectations for healthy life-styles and personal well being. This is surely a time of opportunity for physicians. It is a time of opportunity for reaffirmation and renewal in the medical profession.

In circumstances such as these, there is an expectation of change and a desire to move on to better things, and this desire is clearly evident in health care. One senses a widespread determination somehow to do better with access, quality, efficiency, outcomes, and costs. But no one seems to know quite what to do. There is no real precedent or model to follow. Our nation and our health care needs are too diverse to be well served by any existing model. Our expectations for health and health care may often be unrealistic, but they are real. We find ourselves groping for truly American ways of meeting these very real needs and expectations. How it will all turn out is not yet at all clear, but there is a smell of change in the air, and with change come opportunities for the imaginative and innovative.

Quite appropriately, this is also a time of transition, renewal, opportunity, and, no doubt, innovation, for *The Western Journal of Medicine*. Beginning with the next issue (Volume 153), it will be under the direction of a new editor. Linda Hawes Clever, MD, assumes the editorship of this, the official scientific journal of nine western medical associations. Looking ahead, one may assume that bioscience and biotechnology will contine to progress, that socioeconomic imperatives will continue to have their effect on health care, that ethical issues resulting from medical progress will bring the larger society into closer touch with medical practice and the realities of patient care. One may expect that somehow, because of the unquenchable dedication of individual physicians, medicine will remain a humanitarian calling and not become either a business, focused only on the "bottom line," or simply a trade composed of technicians who market their specialized technical skills to the providers and consumers of health care, however these might come to be defined. But there will be change and, no doubt, progress.

The new editor will find a journal ready to report to its readers on the bioscience and biotechnical advances that will occur; on the fascinating developments that are sure to come about as the art of medicine in patient care becomes more specifically defined in relation to the evolving social, economic, and political health care environment; and on the future interactions of medicine with the larger society, which will become increasingly important as both grapple with human health and even human survival in these extraordinary times.

This retiring editor wishes Dr Clever every success and would remind her that this distinguished journal will celebrate its 100th anniversary in the year 2002, just a few years hence!

MSMW

## Kidney Transplant Revisited (1990)

In the more than 35 years of clinical renal transplantation, significant improvements have been made in this undertaking. Two-year patient and graft survivals of 95% and 80% to 90%, respectively, are generally being realized, and there is an acceptance that renal transplantation is preferable to chronic dialysis for cost as well as quality-of-life considerations. Suranyi and Hall detail the current state of the art of renal transplantation in their article that encompasses many of these advances to the present stage.[1] In describing the present clinical field of transplantation, moreover, the authors point out current and future problems in this endeavor. These problems include pragmatic, social, as well as more theoretic and basic scientific issues.

The first pragmatic problem is one of donor supply. Although renal tranplantation offers the possibility of living donor utilization (in contrast to other solid organs), the long-term risk (that is, risk to donors for more than 20 years after a donor nephrectomy) to such donors has until now not been clearly described. In addition, many living donors turn out not to be physiologically acceptable for donation.[2] Living unrelated donors offer another donor "pool" possibility, but outcomes in the recipients of these sorts of transplants may only approximate the current results of cadaver donor transplantation. It appears that the currently used donor "pool" for cadaver kidneys has a threefold to fourfold shortfall for prospective renal transplant recipients.[3] One useful, practical response has been the coordination of population donor education programs through the United Network of Organ Sharing (UNOS), which encourages cadaver multiorgan donation. With the increasingly improved results with liver, heart, heart-lung, and pancreas transplants—in addition to the historically good, cadaver kidney transplant results—

there has been greater public awareness of the overall need for cadaver-solid organ donations. Efforts will clearly need to be made to further emphasize this need to certain ethnic groups. Last, it is likely that basic immunologic advances will allow the use of xenogenic (cross-species donors and recipients) transplants in the not-so-distant future. Such a basic science breakthrough would certainly answer our current organ shortage problems, which require homografting techniques (using the same biologic species).

A second pragmatic problem has been that of tissue typing. Since Professors Dausset and Terasaki's findings in the 1950s and 1960s, it has long been recognized that HLA matching at the major histocompatibility complex (MHC) loci results in improved graft survival following kidney transplantation.[4] It has proved a problem to have specific and precise antiserum for these important tissue-type testing assays, and there are often large laboratory-to-laboratory variations. These variations prove to be greater for the class II antigen loci testing (or DR "typing"). Crossmatching requires a certain percentage of lymphocytolysis to produce a positive direct crossmatch reading, so that there can be an inherent imprecision when tissue typing persons using current antibody-surface antigen techniques. Attempts to standardize these tests have included cooperative histocompatibility workshops, now sponsored through the American Society of Histocompatibility and Immunogenetics. Newer methods using DNA probes will soon be able to define an individual donor and recipient's MHC type based on nucleotide sequencing. It will be important to transfer this technique from the "bench" to the clinical histocompatibility laboratories so that organ-recipient matching can be more standardly and precisely accomplished throughout the country.

A third practical problem has been organ sharing and organ storage. In the past three years, with federal legislative authorization, local organ procurement agencies have been formed that coordinate educational and clinical aspects of cadaver organ donation in a given geographic area. A national network (UNOS) has served as the coordinating agency for the entire United States. It took many meetings between transplant surgeons, physicians, referring physician groups—specifically, neurosurgeons and emergency or critical care physicians—and nurse coordinators to develop compromises and plans that have reduced the competition of previous individual programs (procurement efforts). Organ sharing currently allows for the placement of many more closely matched grafts than were previously performed. Nonetheless, procurement teams and the transplant surgeons must work with standardized, high-quality surgical-procurement techniques to ensure that there be few technical problems when the organs are transferred between geographic locations. Additional work is now underway to improve any given patient's accessibility to obtaining a cadaver-donated graft and to avoid perceived cadaver waiting-list inequities.[5]

Organ preservation, allowing the time to share as well as time to medically prepare a recipient for the transplant, has continued to develop. The Belzer perfusion solution (UW) has reduced the rate of post-renal transplant acute tubular necrosis from 40% to 15%.[6] Additional work, however, will be needed to reduce the effects from warm ischemia injury on function following cadaver renal transplant. Research involving superoxide dismutase and calcium channel blockers has already shown varying but encouraging results. Efforts directed at a variety of endothelial cell-response mediators following warm ischemic insults may also promise to alleviate the consequences of tissue necrosis.

Kidney transplant efforts have been the beneficiary of a heightened interest in immunology by both the academic and commercial scientific communities over the past 15 years. Besides transplantation, a wide variety of medical problems—oncologic, infectious, arthritic, and dermatologic, to name a few—have stimulated basic research. Pharmaceutical firms have taken an increasingly important role in the development of immunodiagnostic and immunotherapeutic agents (Burroughs Wellcome: azathioprine; Fujisawa: FK 506; Ortho Pharmaceuticals: OKT3; Ortho and Becton-Dickinson: monoclonal diagnostic reagents; Sandoz: cyclosporine; Upjohn: polyclonal antithymocyte globulin; and many other firms). As well, the scourge of the acquired immunodeficiency syndrome in the 1980s, with its primary defect being that of a retrovirus-induced, T-cell immunosuppression, has focused both the National Institutes of Health and public concern towards a medical condition that is principally immunologic. There have been major basic scientific advances over the past eight years in attempts to deal with infection by the human immunodeficiency virus that have yielded "spin-off" discoveries for the management of transplants.

In addition, there is increasing interest in areas of molecular biology. Investigators in transplantation are no longer merely studying an interleukin molecule in the circulation or in the extracellular milieu (such as interleukin 2 [IL-2]); they are characterizing the kinetics of messenger RNA for IL-2 expression (an earlier intracellular step). Researchers want to know not only cellular trafficking but intracellular trafficking of various ions and molecules. Scientists no longer are content with cell type; they are increasingly aware of the importance of the extracellular matrix (which is being noted to be different from tissue to tissue) on which the cells function.

At Stanford, investigators have recently been able to transfer human lympoid tissue to mice and to arrange for this lymphoid transfer to be maintained in the mice progeny.[7] This advance will allow many detailed scientific investigations of the human immune response through carefully controlled laboratory experiments. These molecular biologic findings will offer important insights that will allow the earlier and more precise recognition of rejection, or infection, and of therapeutic responses in graft recipients.

Suranyi and Hall are correct in pointing out that past and current immunosuppressive agents have been irreconcilably linked with greater frequencies of infections and neoplasms. Neoplasms following transplantation are themselves felt to have infectious origins—that is, Epstein-Barr virus and papovavirus-transformed cell lines. Reductions in rejection rates have often been accompanied by immunosuppressive usage that promotes increases in infection rates. Better patient management, prophylactic antibiotic and antiviral regimens, and careful patient preparation have all improved post-transplant infectious morbid outcomes.[8]

Nonetheless, the "dream" of long-term allospecific immunotolerance continues to stimulate the search for more specific immunotherapy. There are important interindividual differences in drug responsiveness (characterized by in vivo and in vitro assays), the application of which might yield more beneficial drug-induced immunotherapy for any given individual transplant recipient.[9] Modification of the allograft

tissue itself before transplantation might also yield a graft with fewer passenger dendritic or leukocyte cells and, by itself, be less antigenically dissimilar, with consequent reduced needs for host immune responses.

A final current and future problem for renal transplantation involves that of recurrent renal disease (usually a form of recurrent glomerulonephritis). We recently reviewed our own experience with more than 700 cyclosporine-treated patients with kidney transplants, and it appears that cyclosporine use did little to reduce the incidence of recurrent focal sclerosing glomerulonephritis, both forms of membranoproliferative glomerulonephritis, as well as IgA nephropathy.[10] In addition, diabetic glomerulopathy often recurs in insulin-dependent diabetic recipients in the five to ten years after a kidney transplant. Further work will be necessary to characterize the immune mechanisms of the various types of glomerulonephritis and work to improve diabetic recipients' glycemic control (with either pancreas transplant, islet cell transplant, or implantable islet reservoirs).

It has been rewarding to observe the improvements in clinical renal transplantation over the past 35 years; yet, one senses that we are only slightly ahead of being the "halfway" technology that Lewis Thomas spoke of in the 1970s.[11] Further advances in the next 10 to 20 years should allow for a fuller realization of curative renal transplantation.

WILLIAM J. C. AMEND, Jr, MD
*Clinical Professor of Medicine*
*University of California, San Francisco, School of Medicine*
*San Francisco*

## REFERENCES

1. Suranyi MG, Hall BM: Current status of renal transplantation. West J Med 1990; 152:687-696
2. Bay WH, Hebert LA: The living donor in kidney transplantation. Ann Intern Med 1987; 106:719-727
3. Soifer BE, Gelb AW: The multiple organ donor: Identification and management. Ann Intern Med 1989; 110:814-823
4. Gilks WR, Bradley BA, Gore SM, et al: Substantial benefits of tissue matching in renal transplantation. Transplantation 1987; 43:669-674
5. Held PJ, Pauly MV, Bovbjerg RR, et al: Access to kidney transplantation—Has the United States eliminated income and racial differences? Arch Intern Med 1988; 148:2594-2600
6. Belzer FO, Southard JH: Principles of solid-organ preservation by cold storage. Transplantation 1988; 45:673-676
7. McCune JM, Namikara R, Kaneshima H, et al: The SCID-hu mouse: Murine model for the analysis of human hematolymphoid differentiation and function. Science 1988; 241:1632-1639
8. Strom TB: Immunosuppressive agents in renal transplantation. Kidney Int 1984; 26:353-365
9. Langhoff E, Ladefoged J: The impact of high lymphocyte sensitivity to glucocorticoids on kidney graft survival in patients treated with azathioprine and cyclosporine. Transplantation 1987; 43:380-384
10. Vincenti F, Biava C, Tomlanovich S, et al: Inability of cyclosporine to completely prevent the recurrence of focal glomerulosclerosis after kidney transplantation. Transplantation 1989; 47:595-598
11. Thomas L: Lives of a Cell. New York, Viking, 1974

# Case Reports

## Acute Pancreatitis Associated With High-Dose Interleukin-2 Immunotherapy for Malignant Melanoma

GEORGE R. BIRCHFIELD, MD
JOHN H. WARD, MD
*Salt Lake City*

BRUCE G. REDMAN, DO
LAWRENCE FLAHERTY, MD
*Detroit*

WOLFRAM E. SAMLOWSKI, MD
*Salt Lake City*

THE LYMPHOKINE INTERLEUKIN 2 (IL-2) has significant antineoplastic activity against metastatic malignant melanomas and renal cell carcinomas. Objective responses have occurred in 20% to 33% of patients treated with high-dose IL-2 plus lymphokine-activated killer cells. Complete remissions have been obtained in about 8% to 15% of treated patients.[1,2] Most of the complete responses have lasted many months, with the longest approaching five years.[1] Unfortunately, the toxicity of IL-2 is substantial and can involve several organ systems. The various side effects of IL-2 have been extensively described by Rosenberg and colleagues.[1-4] Frequent side effects include a pronounced increase in vascular permeability, called the vascular leak syndrome, which is manifested by decreased intravascular volume and peripheral resistance and increases in interstitial fluid. This is clinically manifest by weight gain, edema, hypotension (often requiring pressor therapy), and oliguria. Other important side effects include fever, chills, anemia, and thrombocytopenia. Common toxic effects to the gastrointestinal system include nausea and vomiting, diarrhea, anorexia, elevated liver function tests, and, rarely, spontaneous bowel perforation (< 1% of treated patients).[5] Pancreatitis has not been previously reported with IL-2 therapy.

We describe two cases of probable pancreatitis associated with high-dose bolus IL-2 therapy and provide a brief discussion of the evidence for IL-2 as the etiologic agent.

### Report of Cases

*Case 1*

The patient, a 63-year-old man, had metastatic melanoma to the right inguinal lymph nodes develop in August 1988. Pretherapy staging procedures showed a right inguinal mass and extensive right iliac and para-aortic adenopathy to the level of the diaphragm. There were no visceral metastases. The patient drank alcohol occasionally, consuming about 500 ml of alcohol per month. There was a more substantial history of alcohol consumption in the past. There was no history of previous abdominal operations, gallstones, pancreatitis, or hypertriglyceridemia. The patient was not receiving any medications before the IL-2 therapy.

In October 1988, the patient was treated on a multi-institutional protocol with the administration of high-dose bolus IL-2 without lymphokine-activated killer cells (following the written documentation of informed consent on an institutional review board-approved protocol). He received IL-2 at 100,000 units per kg ($7.3 \times 10^6$ units) intravenously every eight hours for a total of 14 doses. Concomitant medications included acetaminophen, 650 mg every four hours; indomethacin, 50 mg every eight hours; and ranitidine, 150 mg twice a day. During the last six doses of IL-2 and during the following ten days, the patient received furosemide to relieve treatment-related weight gain. Oliguria did not develop (urine output <240 ml during an eight-hour period) and neither did hypotension (systolic blood pressure <90 torr) during IL-2 therapy.

Three days after the last dose of IL-2, fever and marked confusion developed. A computed tomographic (CT) scan of the head and the results of a lumbar puncture were normal. A chest x-ray film showed a left-sided pleural effusion. A thoracentesis established the exudative nature of the effusion. A pleural fluid amylase level was 87 IU per liter. A day later the patient complained of severe left upper quadrant pain. On physical examination his abdomen was distended and had rare bowel sounds. Supine and upright radiographs of the abdomen revealed an ileus with multiple air-fluid levels but no free air. A CT scan of the abdomen was without change from the pretreatment study. The pancreas did not appear edematous. There was no dilatation of the gallbladder or bile ducts, nor were gallstones visualized. A serum amylase level was 75 IU per liter (normal 23 to 185) and a lipase level was 250 IU per liter (normal 0 to 160). A simultaneous creatinine level was 122 μmol per liter (1.6 mg per dl; normal 61 to 107 μmol per liter). The amylase and lipase values increased over the four-day period following the last dose of IL-2 and peaked at 198 IU per liter and 470 IU per liter, respectively. By this time the creatinine level had declined to 84 μmol per liter (1.1 mg per dl). The episode of pancreatitis was treated with bowel rest and narcotics given intravenously with resolution of the abdominal pain three days after it began.

A posttreatment follow-up at two weeks revealed normal serum amylase and lipase values, and he had suffered no further bouts of abdominal pain. Nine weeks after the initiation of therapy, a partial response was documented. The patient refused further IL-2 therapy. His disease has currently stabilized at pretreatment dimensions.

*Case 2*

The patient, a 49-year-old man, was diagnosed to have malignant melanoma metastatic to the left axillary and inguinal lymph nodes. A pretherapy staging evaluation showed

(Birchfield GR, Ward JH, Redman BG, et al: Acute pancreatitis associated with high-dose interleukin-2 immunotherapy for malignant melanoma. West J Med 1990 Jun; 152:714-716)

From the Division of Hematology/Oncology, University of Utah School of Medicine, Salt Lake City (Drs Birchfield, Ward, and Samlowski); the Division of Hematology/Oncology, Wayne State University School of Medicine, Detroit (Drs Redman and Flaherty); and the Veterans Administration Medical Center, Salt Lake City (Dr Samlowski).

This work was supported by Veterans Administration Medical Research Funds, the Utah Regional Cancer Center Core grant No. CA42014, and Clinical Research Center grant No. RR00064 from the National Institutes of Health.

Reprint requests to Wolfram E. Samlowski, MD, Division of Hematology/Oncology, 4C 416 University of Utah Medical Center, Salt Lake City, UT 84132.

ABBREVIATIONS USED IN TEXT

CT = computed tomography
IL-2 = interleukin 2

polycystic renal and hepatic disease but no visceral metastases. There was a history of alcohol abuse in the past, but no history of gallstones, pancreatitis, nor recent abdominal operations. He was taking acetaminophen and aspirin for pain.

In December 1988, the patient was started on a regimen of IL-2 at 100,000 units per kg given intravenously every eight hours (following written documentation of informed consent). Concomitant medications included indomethacin, 25 mg every 8 hours; acetaminophen, 650 mg every 4 hours; and ranitidine, 150 mg every 12 hours. Because of treatment-associated weight gain, furosemide administration was begun on day 5. The patient received all 14 planned doses of IL-2 without hypotension or oliguria.

One day following the last dose of IL-2, the patient began experiencing severe, diffuse abdominal pain, anorexia, nausea and vomiting, and decreased urinary output. An abdominal radiograph showed an ileus. Ultrasonography and CT scan of the abdomen showed an edematous pancreas with peripancreatic and left perirenal fluid. No evidence of gallbladder disease or biliary duct dilatation was seen. The serum amylase and lipase levels were elevated at 44 IU per liter (normal 30 to 110) and 9,633 IU per liter (normal 23 to 208), respectively. The serum creatinine level was 336 $\mu$mol per liter (4.4 mg per dl). As the creatinine level returned to normal, however, the posttreatment serum amylase and lipase levels continued to rise and peaked three days after the onset of pain at 484 and 13,286 IU per liter, respectively. The episode of pancreatitis was treated with bowel rest. Low doses of dopamine were given to treat the oliguria. The patient's symptoms resolved six days after the last dose of IL-2. Treatment with IL-2 was not repeated owing to disease progression.

## Discussion

The diagnosis of acute pancreatitis is based primarily on clinical symptoms and signs, with confirmation by laboratory and radiographic studies.[6-8] The rapid onset of severe and constant abdominal pain, which may radiate to the back, is the classic clinical feature. The pain may last for hours to days. Ileus and pleural effusions are frequently associated clinical findings. Supporting laboratory data for the diagnosis of acute pancreatitis include an elevated serum amylase value, lipase level, or both, and the radiographic finding of an edematous pancreas by ultrasonogram or computed tomography. Conventional abdominal radiographs may also show pleural effusions (usually left-sided) and an ileus.

Symptoms and radiographic findings compatible with the diagnosis of pancreatitis developed in our patients shortly after the administration of IL-2. The first patient should be considered as having probable pancreatitis because of relatively minor elevations of serum amylase and lipase levels, as well as relatively modest pleural fluid amylase levels. This patient's symptoms and signs were compatible with the diagnosis, however, and no alternative explanation, such as bowel perforation or sepsis, could be found, despite an exhaustive evaluation. Our second patient had much more classic pancreatitis. These symptoms and signs were associated with significant elevations of serum amylase and lipase levels. Other common causes of acute pancreatitis, such as a recent abdominal operation, gallstones, hypertriglyceridemia, and malformations of the pancreas, were excluded in our patients. Hypotensive shock, a rare cause of acute pancreatitis, did not occur.[7,8] The elevated serum amylase and lipase values could not be explained on the basis of elevated serum creatinine values because they persisted well after the normalization of serum creatinine values in both patients.

Medications are important etiologic agents in the development of acute pancreatitis. Agents associated with the development of acute pancreatitis include furosemide, estrogens, thiazide diuretics, azathioprine, tetracycline, and sulfonamides. Less well-documented associations of glucocorticosteroids, indomethacin, acetaminophen, and cimetidine with the development of pancreatitis have also been reported.[6] It is possible to see elevated pancreatic enyzme levels and clinical pancreatitis as a protean manifestation of metastatic melanoma. Imaging studies of the abdomen were unable to detect pancreatic metastases in either patient, and subsequent clinical and radiographic observation make pancreatic metastases unlikely.

The time course of the development of the probable pancreatitis observed in our patients tentatively suggests that IL-2 may be either the etiologic or a contributory agent. Withdrawal of the drug coincided with the prompt resolution of symptoms and amylase and lipase elevations. Interleukin 2 is known to be a potent proinflammatory agent, the use of which can result in activation and increased cytotoxicity of lymphocytes.[9] In addition, this agent is known to cause the release of various inflammatory cytokines, such as interleukin 1, tumor necrosis factor, and interferons.[10] An exacerbation of damage to normal tissues in sites of preexisting inflammation has been described in an experimental model of viral myocarditis.[11] It is therefore reasonable to consider that the use of this cytokine might exacerbate chronic or subclinical pancreatic inflammation or might even trigger the injury and immune recognition of normal pancreatic cells.

A contribution of other agents to the development of pancreatitis in our patients cannot be excluded, as both received furosemide, indomethacin, and ranitidine during treatment. These agents may have additive or synergistic properties with IL-2 and could have contributed to the development of pancreatitis. It is interesting to note that both our patients had a previous history of substantial alcohol consumption, although neither had been drinking for a significant period (months to years) before the onset of pancreatitis. Whether previous pancreatic damage predisposes to an IL-2-mediated injury remains conjectural. In neither of our patients was IL-2 therapy readministered (because of refusal and a lack of response, respectively).

Two additional patients treated with IL-2 are known to have had asymptomatic pancreatic enzyme elevations develop (Michael Hawkins, MD, National Cancer Institute, Bethesda, Md, oral communication, May 1989). Three additional patients treated with IL-2 plus $\gamma$-interferon protocols have also had symptomatic pancreatitis develop (M. Hawkins, MD, oral communication and unpublished data, May 1989). These observations suggest that IL-2 treatment may play a role in the development of pancreatitis. The frequency of asymptomatic or symptomatic pancreatic inflammation appears to be very low, as this complication has been reported in less than 1% of patients treated with high-dose IL-2 therapy (more than 600 patients). One patient has been

rechallenged with an identical dose and schedule of IL-2 and γ-interferon without a recurrence of clinical symptoms and signs of pancreatitis or elevations of serum lipase or amylase levels (B.G.R., unpublished data, April 1989).

The acute onset of severe abdominal pain and ileus in patients treated with IL-2 is important because the possibility of spontaneous bowel perforation is a known complication.[5] Our experience, described herein, suggests the inclusion of acute pancreatitis in the differential diagnosis of acute abdominal pain in IL-2-treated patients. A careful physical examination and the appropriate laboratory and radiographic studies should be done to both diagnose acute pancreatitis and exclude spontaneous bowel perforation. Both of our patients responded to the cessation of IL-2 therapy and bowel rest as primary therapeutic maneuvers. We, therefore, recommend conservative therapy for the initial treatment of IL-2-associated pancreatitis. Whether pancreatitis will recur following the rechallenge of patients with IL-2-related pancreatitis with a further course of IL-2 therapy remains to be established.

REFERENCES

1. Rosenberg SA, Lotze MT, Muul LM, et al: A progress report on the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukin-2 or high dose interleukin-2 alone. N Engl J Med 1987; 316:889-897

2. Rosenberg SA, Lotze MT, Muul LM, et al: Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. N Engl J Med 1985; 313:1485-1492

3. Rosenberg SA, Lotze MT, Mule JJ: New approaches to the immunotherapy of cancer using interleukin-2. Ann Intern Med 1988; 108:853-864

4. Lotze MT, Matory YL, Rayner AA, et al: Clinical effects and toxicity of interleukin-2 in patients with cancer. Cancer 1986; 58:2764-2772

5. Schwartzentruber D, Lotze MT, Rosenberg SA: Colonic perforation: An unusual complication of therapy with high-dose interleukin 2. Cancer 1988; 62:2350-2353

6. Mallory A, Kern F Jr: Drug-induced pancreatitis: A critical review. Gastroenterology 1980; 78:813-820

7. Geokas MC, Baltaxe HA, Banks PA, et al: Acute pancreatitis. Ann Intern Med 1985; 103:86-100

8. Potts JR: Acute pancreatitis. Surg Clin North Am 1988; 68:281-299

9. Smith KA: Interleukin-2. Annu Rev Immunol 1984; 2:319-333

10. Gemlo BT, Palladino MA, Jaffe HS, et al: Circulating cytokines in patients with metastatic cancer treated with recombinant interleukin 2 and lymphokine-activated killer cells. Cancer Res 1988; 48:5864-5857

11. Estrin M, Huber SA: Coxsackievirus B3-induced myocarditis: Autoimmunity is L3T4+ T helper cell and IL-2 independent in BALB/c mice. Am J Pathol 1987; 127:335-341

# Rhabdomyolysis and *Staphylococcus aureus* Septicemia in a Man With the Acquired Immunodeficiency Syndrome

ALBERT W. WU, MD
*San Francisco*

KURT BENIRSCHKE, MD
J. ALLEN McCUTCHAN, MD
*La Jolla, California*

MYALGIA IS A COMMON COMPLAINT among patients with the acquired immunodeficiency syndrome (AIDS), particularly those taking zidovudine.[1] Rhabdomyolysis, a clinical syndrome of skeletal muscle injury, is an uncommon but important cause of myalgia and has been associated with staphylococcal septicemia in three patients without AIDS.[2-4] Infection with *Staphylococcus aureus* has been noted with increased frequency in patients with AIDS.[5-7] We report the case of a man with AIDS in whom diffuse myalgia developed and who was found to have *S aureus* septicemia with nonsuppurative rhabdomyolysis.

## Report of a Case

The patient, a 43-year-old homosexual man, had two previous episodes of *Pneumocystis carinii* pneumonia that were successfully treated with regimens of trimethoprim-sulfamethoxazole, pentamidine isethionate, and dapsone-trimethoprim. Eight months before admission, therapy with zidovudine, 250 mg every four hours, was started; after five months the dose was decreased to 100 mg every four hours because of transient granulocytopenia. Other medical problems included depression, recurrent herpes genitalis and labialis, oral candidiasis, and dermatitis.

Four weeks before admission, he received influenza and pneumococcal immunizations. One and a half weeks before admission, he had the development of a nonproductive cough, malaise, and intermittent fever and chills. Four days later he began to have diffuse myalgia and noted difficulty initiating urine flow, with frequency and malodorous, dark urine. He also had painful sores on his tongue and soft palate and diarrhea. Three days before admission a visiting nurse noted a temperature of 39.6°C (103.3°F) and normal findings on a chest examination. The day before admission his muscle pains had so increased that he would not get out of bed. He also had dyspnea on exertion. On the morning of admission he was incontinent of stool and began to hallucinate. At the time of admission his medications included acyclovir sodium, 200 mg five times a day; lorazepam, 2 mg twice a day; and amitriptyline hydrochloride, 75 mg at bedtime.

On physical examination he was drowsy but arousable, with a temperature of 34.4°C (93.9°F), a heart rate of 125 beats per minute, a respiratory rate of 60 per minute, and a systolic blood pressure of 70 mm of mercury. He had acrocyanosis, left-sided rales, diffuse weakness, and pronounced muscle tenderness of the arms and legs. He had no rash, muscle swelling, or cardiac murmurs; his neck was supple and his abdomen showed no abnormalities.

Laboratory tests elicited the following values: a hemoglobin level of 112 grams per liter; leukocyte count of $1.0 \times 10^9$ per liter with 0.05 segmented neutrophils, 0.15 band forms, 0.13 metamyelocytes, 0.01 myelocytes, 0.34 lymphocytes, 0.29 monocytes, and 0.03 eosinophils with toxic granulations and Döhle's bodies; and a platelet count of $103 \times 10^9$ per liter. The prothrombin time was 13.2 seconds with a control of 11.7 seconds, and a partial thromboplastin time was 30.2 seconds with a control of 26.1. Arterial blood gas determinations made while the patient was breathing room

(Wu AW, Benirschke K, McCutchan JA: Rhabdomyolysis and *Staphylococcus aureus* septicemia in a man with the acquired immunodeficiency syndrome. West J Med 1990 Jun; 152:716-719)

From the Robert Wood Johnson/Veterans Administration Clinical Scholars Program (Dr Wu), University of California, San Francisco, and the Departments of Pathology (Dr Benirschke) and Medicine (Dr McCutchan), University of California, San Diego, School of Medicine, La Jolla.

Reprint requests to Albert W. Wu, MD, Robert Wood Johnson Clinical Scholars Program, 350 Parnassus, Rm 407, San Francisco, CA 94117.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

air showed a pH of 7.39, a $Po_2$ of 113 mm of mercury, a $Pco_2$ of 21mm of mercury, with a carbon dioxide content of 14 mmol per liter and an anion gap of 19. A serum sodium level was 133 mmol per liter, potassium 4.4 mmol per liter, urea nitrogen 25 mmol per liter, creatinine 503.9 μmol per liter, glucose 8.7 mmol per liter, calcium 2.1 mmol per liter, phosphate 2.0 mmol per liter, aspartate aminotransferase 303 units per liter, albumin 26 grams per liter, and creatine kinase 11,700 units per liter. The urine was yellow and cloudy with a specific gravity of 1.014, pH 5.0, 1+ glucose, 2+ protein, moderate occult blood, moderate bacteria, rare red blood cells, and 6 to 10 white blood cells per high-power field with no casts. The urine was not examined for myoglobin. A cerebrospinal fluid analysis was unremarkable. A chest roentgenogram showed bilateral patchy infiltrates. An electrocardiogram showed sinus tachycardia with nonspecific ST-T wave changes.

Based on the initial diagnosis of sepsis and rhabdomyolysis, a regimen of cefazolin sodium, 1 gram; ampicillin, 2 grams; and ceftazidime, 2 grams, was given intravenously, and oxygen therapy by nasal cannula was started. He also received 5 liters of intravenous fluid with a urine output of 2.7 liters over 12 hours, but he remained hypotensive and complained of severe myalgia. A second laboratory examination showed the urea nitrogen level to be 23.9 mmol per liter, creatinine 389 μmol per liter, carbon dioxide content 9 mmol per liter, magnesium 0.91 mmol per liter, aspartate aminotransferase 628 units per liter, lactate dehydrogenase 111 units per liter, and creatine kinase 33,780 units per liter. His respirations ceased 12 hours after admission, and, in accordance with his previous request, he was not resuscitated.

Penicillinase-positive *Staphylococcus aureus,* sensitive to cefazolin, nafcillin, and gentamicin, grew from blood and urine (greater than $10^5$ colonies per milliliter) and from postmortem cultures of specimens of lung and prostate. Viral cultures of prostate, brain, muscle, and lung were negative for influenza, cytomegalovirus, adenovirus, and enterovirus.

On postmortem gross examination there were pulmonary edema with bilateral pleural effusions, splenomegaly, left pyelonephritis, and prostatic abscesses. There was no muscle edema, hemorrhage, or degeneration, but the skeletal muscle appeared unusually dry. The heart was normal with coronary arteries free of atherosclerosis. Microscopic examination of the lung revealed scattered foci of *P carinii,* as well as cytomegalic cells. There were many renal abscesses. No myoglobin was seen. The prostate showed acute and chronic prostatitis with fibrosis, multiple abscesses, and many bacterial colonies. Cytomegalic cells, necrosis, and inflammation were seen in the central cortex of both adrenal glands. The bone marrow showed evidence of regeneration. There was widespread acute degeneration of skeletal muscle with loss of cross-striations and fragmentation of fibers. Neither inflammation nor organisms were seen (Figure 1). The final diagnosis was AIDS with *S aureus* septicemia, pyelonephritis, prostatitis, and Zenker's hyaline degeneration of muscle.

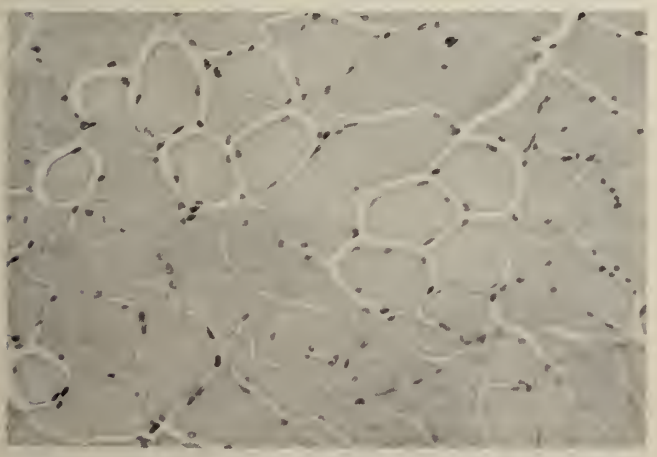


**Figure 1.**—A skeletal muscle biopsy shows fragmented fibers and hyalinized fibers lacking in cross-striations. No inflammation or organisms are present (hematoxylin and eosin; original magnification × 400).

## Discussion

Myalgia is a common complaint among patients infected with the human immunodeficiency virus (HIV). In the phase II placebo-controlled trial of zidovudine in patients with AIDS and AIDS-related complex, myalgia was reported in 11% of patients who were taking zidovudine and 3% of those taking a placebo.[1]

Rhabdomyolysis is a clinical and laboratory syndrome resulting from skeletal muscle injury and the release of muscle cell contents into the plasma.[8] Evidence of rhabdomyolysis in this patient was the extreme elevation of creatine kinase levels and diffuse myalgia without apparent cardiac or brain injury. Acquired causes of rhabdomyolysis include excessive activity, direct muscle injury, ischemia, polymyositis, metabolic disorders, drugs, toxins, and infections. Rhabdomyolysis is an important cause of myalgia, though there is no evidence to suggest that it is more common in AIDS patients than in others.

There were several possible causes of rhabdomyolysis in our patient. While influenza infection is a recognized cause of rhabdomyolysis, influenza immunization is not, and it seems unlikely that influenza immunization was related to his subsequent illness.[8] His symptoms developed more than two weeks after immunization, and while convalescent-phase viral titers were not obtainable, viral cultures were negative for influenza and other viruses. Polymyositis has been described in cases of AIDS,[9] but in this case pathologic findings failed to support this diagnosis. Zidovudine therapy has been associated in four patients with a noninflammatory myopathy of an insidious onset.[10] In contrast, our patient had the sudden occurrence of myalgia that accompanied symptoms of acute infection. Profound hypotension may cause muscle ischemia with rhabdomyolysis,[8] and our patient was hypotensive in the last stages of his illness. His blood pressure was recorded as normal after the myalgia began, however.

We think staphylococcal bacteremia caused our patient's rhabdomyolysis and should be considered when AIDS patients present with this syndrome. Patients infected with HIV may be at an increased risk for staphylococcal infection. *Staphylococcus aureus* was reported by Whimby and coworkers in 32% of episodes of bacteremia among AIDS patients.[5] These cases occurred in association with *P carinii* pneumonia and pulmonary or cutaneous Kaposi's sarcoma.

*Staphylococcus aureus* accounted for 40% of cases of community-acquired bacteremia reported by Witt and colleagues[6]: all of these patients were intravenous drug users, however, making interpretation of causality difficult. Jacobsen and associates found that *S aureus* bacteremia was 20 times more likely to develop in patients with AIDS and AIDS-related complex than in age-matched controls with no risk factors for HIV infection.

The host defense against *S aureus* depends primarily on an intact phagocytic system and is compromised by granulocytopenia or by defective chemotaxis, phagocytosis, or intracellular killing. Cell-mediated immunity may modulate defenses against staphylococcal infection. Skin integrity is also important. In HIV-infected patients, a number of defects may contribute to an increased incidence of staphylococcal infection. Malnutrition, which is common in advanced HIV disease, may increase the susceptibility to infection including *Staphylococcus* species.[11] The high incidence of chronic, pruritic dermatologic disease in patients with HIV infection may provide a portal of entry for staphylococci that colonize the skin. Patients with Kaposi's sarcoma may have an increased incidence of staphylococcal infection if lesions erode or produce local lymphatic obstruction.[5] Granulocytopenia may be caused by zidovudine therapy[1] or complications of HIV infection.[12] Decreased chemotaxis of neutrophils[13] and monocytes[14] has also been observed in AIDS patients. In the absence of obvious malnutrition, dermatitis, granulocytopenia, or Kaposi's sarcoma, the latter mechanism remains the most plausible contributor. Staphylococci, however, are sufficiently virulent to invade apparently uncompromised patients.

There are several possible mechanisms by which *S aureus* infection might cause rhabdomyolysis. Skeletal muscle damage with *S aureus* usually occurs as a suppurative myositis: either as a large, localized abscess or many small abscesses. This condition usually occurs without sustained bacteremia and has been called pyomyositis.[15] Our patient had no evidence of staphylococcal invasion of muscle. Rhabdomyolysis has been seen in patients with toxic shock syndrome,[16-19] presumably due to effects of the exotoxin on muscle, but our patient did not appear to have this syndrome because he lacked the characteristic desquamating rash. We think that *S aureus* caused rhabdomyolysis in our patient through a nonsuppurative process, perhaps due to a different exotoxin.

Three previous cases of rhabdomyolysis associated with staphylococcal septicemia have been reported in patients without toxic shock. Adamski and co-workers described the case of a 15-year-old boy with nonsuppurative myositis and rhabdomyolysis.[2] The creatine kinase level was 33,400 units per liter. Gram-positive cocci were visible around some muscle fibers and *S aureus* grew on cultures. Lannigan and colleagues reported a fatal case of staphylococcal septicemia in a 70-year-old man.[3] A peak creatine kinase level was 83,000 units per liter, and a skeletal muscle biopsy specimen revealed multiple small areas of necrosis with microcolonies of *S aureus*, widespread muscle necrosis, and minimal inflammatory response. They hypothesized that a toxin plays a role in rhabdomyolysis. Saitoh and associates described endocarditis in a 20-year-old man who presented with fever, rash, generalized myalgia, and muscle weakness.[4] Blood and urine cultures were positive for *S aureus*, and a peak creatine kinase level was 990 units per liter. A muscle biopsy specimen showed focal necrosis and mild inflammation without bacterial invasion or suppuration. Saul and co-workers reported an additional case of a 13-year-old girl with rhabdomyolysis with a creatine kinase level of 59,729 units per liter and nonoliguric renal failure, who did not have toxic shock syndrome or bacteremia, but who had *Staphylococcus* organisms isolated from the urine.[20]

Our case differed from those previously reported in that it involved a patient with AIDS, and neither rash nor bacterial invasion of muscle was seen. This also appears to be the first case of Zenker's hyaline degeneration in association with staphylococcal infection, although the case reported by Saitoh and associates may have been another example. Nonsuppurative muscle damage from staphylococcal infection may be more likely to develop in AIDS patients, though this has not been studied.

Zenker first described in 1859 and 1862 the waxy or hyaline degeneration of skeletal muscle in 120 patients who died of typhoid fever.[21(p1580),22] Zenker's hyaline degeneration may occur in any muscle but is most common in the large muscles of the trunk, pelvis, and shoulder girdle. The muscle is grossly very pale. On microscopic examination, there is cloudy swelling of the fibers with a loss of striations and fragmentation into horizontal segments. Sarcolemmal nuclei are slightly swollen and may proliferate. After the first week, highly refractile, eosinophilic, cylindric masses may be seen within the muscle fibers. Hyaline segments are usually interspersed with healthy fibers. Phagocytic cells appear between fibers, but inflammatory cells are never prominent. The proposed mechanism of damage is either a microbial toxin or metabolic disorder in the muscle fibers induced by the infection. In addition to typhoid fever, a high incidence of Zenker's hyaline degeneration was also reported in smallpox. Because these associated diseases are rare in industrialized nations, Zenker's degeneration is an infrequent pathologic finding. It has been described less often in patients with other infectious diseases, including influenza, pneumonia, scarlet fever, diphtheria, tuberculosis, tetanus, cholera, hepatitis A, yellow fever, streptococcal septicemia, and noninfectious diseases such as advanced malignancy and cirrhosis.[22]

## REFERENCES


1. Richman DD, Fischl MA, Grieco MH, et al: The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: A double-blind, placebo-controlled trial. N Engl J Med 1987; 317:192-197

2. Adamski GB, Garin EH, Ballinger WE, et al: Generalized nonsuppurative myositis with staphylococcal septicemia. J Pediatr 1980; 96:694-697

3. Lannigan R, Austin TW, Vestrup J: Myositis and rhabdomyolysis due to *Staphylococcus aureus* septicemia. J Infect Dis 1984; 150:784

4. Saitoh H, Yoshii F, Ishihara T, et al: Rhabdomyolysis associated with staphylococcal septicemia. Rinsho Shinkeigaku 1986; 26:693-697

5. Whimby E, Gold JWM, Polsky B, et al: Bacteremia and fungemia in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1986; 104:511-514

6. Witt DJ, Craven DE, McCabe WR: Bacterial infections in adult patients with the acquired immune deficiency syndrome (AIDS) and AIDS-related complex. Am J Med 1987; 82:900-906

7. Jacobsen MA, Gellerman H, Chambers H: *Staphylococcus aureus* bacteremia and recurrent staphylococcal infection in patients with AIDS and ARC (Abstr). 4th International Conference on AIDS, Stockholm, 1988, p 399

8. Gabow PA, Kaehny WD, Kelleher SP: The spectrum of rhabdomyolysis. Medicine (Baltimore) 1982; 61:141-152

9. Dalakas MC, Pezeshkpour GH, Gravell M, et al: Polymyositis associated with AIDS retrovirus. JAMA 1986; 256:2381-2383

10. Bessen LJ, Greene JB, Louie E, et al: Severe polymyositis-like syndrome associated with zidovudine therapy of AIDS and ARC (Letter). N Engl J Med 1988; 318:708

11. Keusch GT: Malnutrition and infection, *In* Braude A (Ed): Infectious Disease and Medical Microbiology. Philadelphia, WB Saunders, 1986, pp 709-714

12. Lane CH, Fauci AS: Immunologic abnormalities in the acquired immunodeficiency syndrome. Annu Rev Immunol 1985; 3:477-500

13. Nielsen H, Kharazmi A, Faber V: Blood monocyte and neutrophil functions in the acquired immune deficiency syndrome. Scand J Immunol 1986; 24:291-296

14. Prince HE, Moody DJ, Shubin BI, et al: Defective monocyte function in acquired immune deficiency syndrome (AIDS)—Evidence from monocyte-dependent T-cell proliferative system. J Clin Immunol 1985; 5:21-25

15. Armstrong JH: Tropical pyomyositis and myoglobinuria. Arch Intern Med 1978; 138:1145-1146

16. McKenna UG, Meadows JA, Brewere NS, et al: Toxic shock syndrome, a newly recognized disease entity—Report of 11 cases. Mayo Clin Proc 1980; 55:663-672

17. Chesney RW, Chesney PJ, Davis JP, et al: Renal manifestations of the staphylococcal toxic-shock syndrome. Am J Med 1981; 71:583-588

18. Scobie BA: Staphylococcal toxic shock: Two fulminant cases with recovery. NZ Med J 1982; 95:145-147

19. Bachhuber R, Parker RA, Bennet WM: Acute renal failure in toxic shock syndrome owing to rhabdomyolysis. Ann Clin Lab Sci 1983; 13:25-26

20. Saul RA, Vernon M, Roe C, et al: Rhabdomyolysis in a patient with nonoliguric renal failure: Similarities to the toxic-shock syndrome. South Med J 1980; 73:261-263

21. Kaufmann E: Lehrbuch der speziellen pathologischen Anatomie, Vol 2. Berlin, De Gruyter, 1922, p 1580

22. Kakulas BA: Diseases of Muscle. Philadelphia, Harper & Row, 1985, pp 590-594

# Capgras's Syndrome Associated With Sensory Loss

STEPHEN F. SIGNER, MD
*San Diego*

PAUL C. VAN NESS, MD
*Cleveland*

R. JEFFREY DAVIS, DO
*Rancho Mirage, California*

THE CAPGRAS SYNDROME is the delusion that a known person or object has been replaced by a virtually identical duplicate. Reported formally first by Capgras and Réboul-Lachaux as the delusion of doubles ("l'illusion des sosies"), more than 300 cases have been recorded in the English and French literature. The delusion has been found in cases of both idiopathic and secondary ("organic") psychoses.[1] It and several variants form the delusion of substitution[2] or the delusional misidentification syndromes.[3] While sensory loss is frequently cited as one initiator of hallucinations and delusions, a persistent circumscribed delusion of the Capgras type has not been reported in such cases, aside from that of a profoundly deaf man with a progressive dementia.[4]

## Report of Cases

*Case 1*

The patient, a 75-year-old right-handed woman, believed that her spouse of 25 years had been replaced by another man; there has been some gradual accommodation to the "new man's" presence over a two-year period since the symptoms began. Although at least one other object (a bed) had been replaced, she did not think that her maid, natural and stepchildren, or friends had been affected. She believed her house was not the same one she left before being admitted to a hospital, describing it as being larger, having a different layout, and with stairs in places that did not exist previously. She was convinced that her original house and those of neighbors were really one block away and that she could "see" them when she walked by.

The patient had been healthy until four years before when giant cell arteritis developed. Over a two-week period she went blind in the right eye and had severe visual impairment in the left. On high doses of corticosteroids, *Aspergillus* species pneumonia developed from a dormant non-acid-fast pulmonary infection, and the left eye became infected, leading to complete blindness.

About 20 months after her illness began, she was not using any medication and was mildly to moderately depressed, with a sense of helplessness, weight loss, and apathy, but no suicidal ideation; there was no disorder of thought form. Attention, language, calculations, visual-spatial ability, and general fund of knowledge were intact; short-term memory only was mildly impaired. The cranial nerves were normal aside from absent light perception; the results of motor, cerebellar, and sensory examinations were normal. The electroencephalogram showed mild abnormalities with a posterior dominant rhythm of 7 Hz and generalized slowing of background frequencies; a computed tomographic scan showed mild generalized cerebral atrophy and slight enlargement of the ventricles, consistent with her age, but no evidence of a focal lesion. There was no change in her state despite a brief trial of antidepressants, although the depression has remitted somewhat with time.

*Case 2*

The patient, a 66-year-old widow, claimed to have last seen her daughter 18 months before evaluation, but reported hearing her voice intermittently, telling her how she was being tormented by her captors. She believed that her daughter had been hidden in a secret chamber next door and that "a woman" working at city hall pretended to be her daughter. The patient was terrified because her granddaughter had betrayed her own mother by living with the "imposter."

Her belief that her daughter had been replaced began 15 years earlier after surgical treatment of an ear infection eliminated her hearing in both ears; her daughter's voice was heard only on the right and became louder and more persistent after she removed her hearing aid on that side. No other delusional or affective symptoms were ascertainable. The patient had had insulin-dependent diabetes mellitus since age 30, as well as coronary artery disease and peripheral neuropathy. Although anxious and vociferous in her complaints, she had no cognitive impairment noted on examination and there was no history of social deterioration. She did not agree to further assessment or treatment and was released from hospital.

## Discussion

Both patients demonstrated the Capgras syndrome, which appeared some time after a severe sensory loss, accompanied by hallucinations in the affected modality. In patient 1, the delusion persisted even though her medical and psychological state, aside from the residual blindness, had essentially returned to normal; the mild dysrhythmia has been found in some other cases of the syndrome. She had a co-existent symptom of reduplicative paramnesia. In the second patient, the long-term nature and lack of social deterioration suggested that her delusion was circumscribed, so that a diagnosis of late-onset paraphrenia could be considered. The

(Signer SF, Van Ness PC, Davis RJ: Capgras's syndrome associated with sensory loss. West J Med 1990 Jun; 152:719-720)

From the Department of Psychiatry, University of Ottawa School of Medicine and the Royal Ottawa Hospital, Ontario, Canada (Dr Signer); the Department of Neurology, The Cleveland Clinic Foundation, Cleveland (Dr Van Ness); and the Neurobehavior Unit, Canyon Springs Hospital, Rancho Mirage, Southwood Hospital, Chula Vista, California.

Reprint requests to Stephen F. Signer, MD, Neurobehavioral Program, Southwood Hospital, 330 Moss St, Chula Vista, CA 92011.

delusions and reorganization of cognitions in both patients seem to have been maintained by the underlying hallucinations due to sensory loss, even though these emerged during the course of other medical and psychological conditions.

Formed, organized, vivid, and intricate auditory (musical) hallucinations associated with deafness have been reported. The patients were middle-aged or older with at least ten years of hearing impairment, although the hallucinations began suddenly.[5] The Charles Bonnet syndrome refers to the appearance of formed visual hallucinations in the elderly with decreased visual acuity in spite of normal mental functions.[6] De Morsier, however, who named the syndrome, basing his views on a series of cases with a wide variety of pathologic disorders, did not think ocular disease alone was responsible for the phenomena. Both syndromes have been attributed to the loss of sensory information that normally suppresses nonessential information and acquired perceptions (perceptual deficit hallucinations).

Experiments in sensory deprivation produced a state marked by the progressive slowing in mean $\alpha$-frequency with the appearance of $\delta$- and excessive $\theta$-activity in the temporal lobes; increased arousal; and difficulty in maintaining logical, directed thought.[7,8] The reduction of the intensity and patterning of stimuli resulted in hallucinations developing after two to three days and continuing for as long as two weeks.[9] The hallucinations began with simple unstructured forms and progressed over time to complex, structured, meaningful imagery.[8] It is still unclear how the hallucinations generalize in their effects, but there was a significant association between a paranoid disorder and bilateral conductive deafness, particularly with an earlier onset, longer duration, and greater severity.[10] Increasing external auditory stimulation (by means of radio headphones) helps to decrease or control chronic auditory hallucinations[11] in schizophrenia.

Horowitz has examined hallucinations as a final common pathway of the processes of image representation.[12] These processes were hypothesized to include intensifications of internal input (possibly from the relative reduction of external input or augmentation of the activity of the representational system), impaired information processing, and lapses in control over internal information to image systems (as a transformation of affective states). Particular cognitive attributes or mechanisms may increase the risk of the appearance of hallucinations. Goldstone and Sarbin have independently proposed that internal sensations interpreted in a nonpreferred sensory mode may be more easily misrepresented because the patient is not accustomed to imagery in that mode and may assume that the sensations have an external origin.[13,14] Patients with auditory hallucinations show a reduced preference for auditory imagery and are less capable than other psychiatric patients of recognizing verbatim recordings of their thoughts after one week. They are less able to delay the assignment of meaning to ambiguous stimuli and to consider alternative meanings, which reduces the quality of their perception by introducing errors of premature judgment.[15]

Sensory deficits probably contribute substantially to the development of hallucinations, and possibly delusions in the elderly without previous psychotic symptoms, which can become long-lasting, stable psychopathologic features. Other focal or diffuse changes may become coupled with aberrant sensory information with consequent "misprocessing" and misinterpretation or a loss of the ability to correctly monitor cues from the environment. The Capgras syndrome is among the many forms this disturbance may take.

## REFERENCES


1. Berson RJ: Capgras' syndrome. Am J Psychiatry 1983; 140:969-978
2. Signer SF: Capgras' syndrome: The delusion of substitution. J Clin Psychiatry 1987; 48:147-150
3. Christodoulou GN: The Delusional Misidentification Syndromes. Basel, Karger, 1986
4. Wrigley M: Capgras' syndrome in a patient with dementia. Br J Psychiatry 1987; 151:273-274
5. Raghuram R, Keshavan MD, Channabasavanna SM: Musical hallucinations in a deaf middle-aged patient. J Clin Psychiatry 1980; 41:357
6. Rosenbaum F, Harati Y, Rolak L, et al: Visual hallucinations in sane people: Charles Bonnet syndrome. J Am Geriatr Soc 1987; 35:66-68
7. Goldberger L: Sensory deprivation and overload. *In* Goldberger L, Breznitz S (Eds): Handbook of Stress: Theoretical and Clinical Aspects. New York, Free Press, 1982
8. Zuckerman M: Perceptual isolation as a stress situation. Arch Gen Psychiatry 1964; 11:255-276
9. Solomon P, Laderman H, Mendelson J, et al: Sensory deprivation: A review. Am J Psychiatry 1957; 114:357-363
10. Cooper AF, Curry AR: The pathology of deafness in the paranoid and affective psychoses of later life. J Psychosom Res 1976; 20:97-105
11. Birchwood M: Control of auditory hallucinations through occlusion of non-aural auditory input. Br J Psychiatry 1986; 149:104-107
12. Horowitz M: A cognitive model of hallucinations. Am J Psychiatry 1975; 132:789-795
13. Goldstone S: Psychotropics, reality, and hallucinations. *In* West JW (Ed): Hallucinations. New York, Grune & Stratton, 1962
14. Sarbin TR: The concept of hallucination. J Personality 1967; 35:359-380
15. Heilbrun AB, Blum NA: Cognitive vulnerability to auditory hallucinations: Impaired perception to meaning. Br J Psychiatry 1984; 144:508-512

# Correspondence

## Patients' Presence in Prenatal Screening

To THE EDITOR: I found the epitome, "Advances in Prenatal Screening," by Ganiats and Baughan in the March issue interesting but puzzling.[1] There appear to be two parallel ways of thinking about prenatal care issues: patient-centered and technologic. The "public health" approach as described by Ganiats and Baughan represents the technologic approach exclusively. Education of the patient as to important issues in managing her own pregnancy is not even considered. Certainly, they have covered nicely all the tests to do at what point in pregnancy, but patients and physicians get into trouble because of what patients do or do not do, or what physicians tell them or do not tell them, and how the communication goes wrong. When an outcome is bad, technology often does not help the mother or the physician, only the malpractice attorney. Let's get the *patient* back into "advances in prenatal screening."

BERTHOLD E. UMLAND, MD
*Associate Professor*
*Dept of Family, Community, and Emergency Medicine*
*University of New Mexico School of Medicine*
*2400 Tucker Ave, NE*
*Albuquerque, NM 87131*

REFERENCE

1. Ganiats TG, Baughan DM: Advances in prenatal screening. *In* Epitomes—Important Advances in Clinical Medicine—Preventive Medicine and Public Health. West J Med 1990; 152:285

## *Blastocystis hominis*

To THE EDITOR: Babb and Wagener, in their retrospective study of *Blastocystis hominis* in the November 1989 issue,[1] compare their findings with ours[2] and come to the opposite conclusion, namely that "*B hominis* is a potential pathogen that can in some patients lead to diarrhea and abdominal pain." Let us examine the basis on which they base this not-very-emphatic endorsement of its pathogenicity.

Some 3% of 2,700 patients who had stool examinations done during a one-year period were found to have *B hominis* in their stools. Of medical records examined, 65 contained relevant clinical information. Of these 65, however, fewer than three stool specimens were submitted by 24 persons. Sawitz and Faust, whose exhaustive study is still our only guide in this regard, conclude that only about two thirds of *Entamoeba histolytica* infections are discovered in two stool examinations, by a combination of techniques including but not limited to stained slides.[3] The other 41 patients had at least three stool examinations, which by Sawitz and Faust's calculations would reveal about 80% of such infections. There are no comparable statistics for *Dientamoeba fragilis* and *Giardia lamblia*. Our own experience, based on patients who had a minimum of six stool examinations, each examined not once but by two licensed microbiology technologists and one of us (E.K.M.), showed it was possible to miss *Giardia* on six such consecutive examinations. Thus, we can conclude that it is probable that some of these 65 patients had undetected amebic or flagellate infections.

In this study, about half (33 of 65) received no treatment, either because they were asymptomatic from the start or because their symptoms cleared up promptly. Of the remaining 32, half (16) had recognized parasites. Both *E histolytica* and *Giardia* respond to treatment with metronidazole, and dientamoebiasis is often asymptomatic. Thus, nothing can be concluded from the favorable response of these 16 patients.

There remain 16 patients who were proper subjects for the study. How many of these had even three stool examinations we do not know, but only 3 of them had even a single follow-up examination. Most became asymptomatic after treatment (it is impossible to tell how many because the authors do not differentiate between the two different patient groups), but these statistics do not justify any conclusions as to the pathogenicity of *B hominis*. Although costly and time-consuming, an adequate number of stool examinations must be done—and preferably checked as we did by several persons—with an adequate number of follow-up examinations after treatment, before drawing any conclusions as to the pathogenicity of an organism whose appearance in the stools of a symptomatic person may be as coincidental as that of *Entamoeba coli* or *Endolimax nana*. Babb and Wagener imply that we consider "functional bowel syndrome" as a convenient catch-all for those patients with *B hominis* in whom we were unable to find recognized pathogens. On the contrary, all those to whom this diagnosis was assigned fulfilled all the recognized criteria for this diagnosis at follow-up examinations for an average of 30 months.

Most of the articles cited by Babb and Wagener are single-case reports. They do not mention the work of Miller and Minshew,[4] who were unconvinced of the pathogenicity of *Blastocystis* on the basis of their own study of 11 patients and a review of the literature, or that of Chen and co-workers,[5] who by using immunoblot analysis were unable to detect any serologic response from four patients with a diarrheal syndrome associated with the presence of *B hominis*, in contrast to what is seen with known intestinal pathogens such as *Giardia*.

EDWARD K. MARKELL, PhD, MD
MICHAEL P. UDKOW, MD
*Department of Medicine*
*Kaiser Foundation Medical Center*
*280 W MacArthur Blvd*
*Oakland, CA 94611*

REFERENCES

1. Babb RR, Wagener S: *Blastocystis hominis*—A potential intestinal pathogen. West J Med 1989; 151:518-519

2. Markell EK, Udkow MP: *Blastocystis hominis*: Pathogen or fellow traveler? Am J Trop Med Hyg 1986; 35:1023-1026

3. Sawitz WG, Faust EC: The probability of detecting intestinal protozoa by successive stool examinations. Am J Trop Med 1942; 22:131-136

4. Miller RA, Minshew BH: *Blastocystis hominis*: An organism in search of a disease. Rev Infect Dis 1988; 10:930-938

5. Chen J, Vaudry WL, Kowalewska K, et al: Lack of serum immune response to *Blastocystis hominis* (Letter). Lancet 1987; 2:1021

## Espresso Maker's Wrist

To THE EDITOR: Food service workers are subject to a variety of cumulative trauma disorders, including carpal tunnel syndrome (grocery checkers) and pressure neuropathy of the deep palmar branch of the unlar nerve ("pizza cutter's palsy").[1,2] Reported here is a case of de Quervain's tenosynovitis in a novel occupational context.

A 41-year-old restaurant owner was noted by this physician-customer to be wearing an elastic bandage on his right (dominant) wrist. Upon inquiry, he reported a two-month history of gradually increasing pain of the radial aspect of the joint. The pain was exacerbated each time he inserted spigots

containing fresh coffee grounds into an espresso machine with a rotating motion of the handle—a maneuver that he repeated 80 to 100 times a day. When doing this task, he would grasp the spigot handle with his supinated right hand, rotating the handle to his right with an abrupt ulnar deviation of the wrist. He had no previous injuries involving the right upper extremity and had no history of arthritis or tendinitis. He had elected to use the elastic wrap without medical consultation and reported only minimal improvement with its use.

On examination the wrist was moderately tender over the abductor pollicis longus. No erythema or swelling was apparent, and there was no crepitus over the radial border of the wrist with thumb abduction. Sensory and motor function in the hand was intact. The result of a Finkelstein's test, however, was positive. The patient was informed that he had early de Quervain's tenosynovitis. He was advised to rest the affected part, to take an over-the-counter nonsteroidal anti-inflammatory medication, and to consider obtaining a wrist splint. After three weeks' rest and medication, symptoms were almost entirely resolved. He adapted to this occupational disability by using his opposite hand to insert spigots into the espresso machine, taking care to avoid any abrupt or strenuous maneuvers in the process. There has been no recurrence of symptoms in the intervening three months.

De Quervain's tenosynovitis has been noted occupationally in association with repetitive hand movements—historically in "washerwoman's sprain," involving the wringing of clothes, and more recently in assembly-line work.[3] While the prevalence of this disorder among espresso makers is unknown, the recent surge in popularity of espresso drinking may place additional persons at risk. Physicians indulging in this dietary habit should maintain a high degree of vigilance for affected workers and suggest alternative work practices when appropriate.

DENNIS SHUSTERMAN, MD, MPH
*PO Box 9116*
*Berkeley, CA 94709*

REFERENCES

1. Barnhart S, Rosenstock L: Carpal tunnel syndrome in grocery checkers. West J Med 1987; 147:37-40

2. Jones HR Jr: Pizza cutter's palsy (Letter). N Engl J Med 1988; 319:450

3. Armstrong TJ, Fine LJ, Goldstein SA, et al: Ergonomic considerations in hand and wrist tendinitis. J Hand Surg 1987; 12:830-837

## A Pathologist's View of Mohs' Micrographic Surgery

To the Editor: As a pathologist, I find several major problems with the article by Darmstadt and Steinman in the February issue reviewing the use of Mohs' micrographic surgery.[1] First, the amount of tissue that can be placed on a cryostat chuck is generally less than 1 cm in diameter and less than 0.5 cm thick; therefore, large specimens require, in many cases, hours to orient, incise, divide, ink, and properly process and interpret. Second, while this parallel margin concept is theoretically sound, in real practice it is impossible to obtain a truly flat surface that is exactly parallel to the cryostat's cutting blade. Therefore, one actually "faces off" or cuts through the margin to obtain an appropriate flat sheet of tissue to place on the glass slide. Hence, one is not looking at the actual margin but at a layer of tissue that is generally from one to several millimeters away from the margin. Third, anyone who has substantial experience interpreting frozen sections is aware that there are frequently instances where dysplastic dermal adnexal structures may be mistaken for nests of malignant epithelium. The Mohs technique does not allow the relationship between these nests and the overlying epidermis to be seen. Also, the so-called permanent or deeper sections are even farther from the true surgical margin than is the frozen section slide. In contrast, classic perpendicular sections allow one to see not only whether the margin is involved but how close to the margin any tumor resides, and deeper sections into the paraffin block do not destroy this relationship as is the case with the Mohs technique.

As stated in the article, it may be a "unique" feature of this technique that a surgeon is involved in "all phases of the procedure," but this may not be cause for embracing the procedure. Just as a pathologist does not do surgical procedures as competently as a surgeon, I seriously doubt that a surgeon is as qualified as a pathologist to make histopathologic diagnoses on frozen section, particularly if an unexpected lesion is seen. Metastatic renal cell carcinoma, metastatic breast carcinoma, and many other lesions that dermatologists have very little experience recognizing may be present in the skin. While in some ways I would welcome dermatologists taking over this time-consuming and often frustrating process and while the Mohs technique may be appropriate in a rare case, I hope that the disadvantages of this extremely labor-intensive, expensive technique are properly appreciated by your readers.

RICHARD E. SAFRIN, MD
*Department of Pathology*
*Alvarado Hospital Medical Center*
*6655 Alvarado Road*
*San Diego, CA 92120*

REFERENCE

1. Darmstadt GL, Steinman HK: Mohs' micrographic surgery of the head and neck. West J Med 1990; 152:153-158

## Ruminations of an Aspiring Californian

To the Editor: In recent years, the list of health problems attributable to life-style has grown beyond those due to diet, physical activities, and noxious substances. We report a case of acute airway obstruction associated with two relatively recent trends: adult orthodontics and California cuisine.

Not long after moving to California from the East Coast, on the advice of her dentist and with the encouragement of a Southern California specialist in adult orthodontics, a 31-year-old woman began a course of orthodontia to correct malocclusion. Treatment progressed with exemplary results and her bands were removed. She received a removable retainer that fit beneath her hard palate and was instructed to wear it even while eating.

At a lunch meeting, while discussing the benefits of a low-fat diet over a platter of al dente vegetables, she suddenly stood and raised both hands to her neck in the international sign of choking. Her companion did a prompt Heimlich maneuver, ejecting an intact, nearly raw two-inch-long piece of broccoli. The broccoli had lodged in her pharynx between her trachea and the back of the retainer, completely occluding the airway.

To our knowledge, this is the first report of choking associated with an orthodontic appliance. Patients should consider removing their retainers before eating.

ALBERT W. WU, MD
HAYA R. RUBIN, MD, PhD
*University of California, San Francisco, School of Medicine*
*350 Parnassus Ave, Rm 407*
*San Francisco, CA 94117*

## Putting Practice Into Law

To the Editor: I read with interest the discussion on "Physician Risk and Responsibility in the HIV Epidemic" by Dr Molly Cooke in the January issue.[1] Her review was both cogent and concise, but I find it lamentable that she neglected to point out that in spite of our vaunted professionalism and high ethical standards, there is no societal guidance, incentive, or even concern for such matters embodied in the legal foundation of our profession—the Medical Practice Act. As a former member of the Board of Medical Quality Assurance, I am very familiar with the necessary but rather mundane matters within the authority of the medical board as outlined by Dr Kardos in the same issue.[2] Now more than ever, as cultural coherence seems to be slipping away, as physicians become more masters of technology than ministers of human kindness, as spiritual and ethical matters are more pontificated than practiced, I think it is long overdue that public policy should embody codes of responsibility for its physicians in return for the granting of a license, and such issues as treatment without discrimination according to race, sex, or religion (which we all accept), as well as without regard to disease process (within the realm of competence) or regardless of ability to pay or type of insurance should be embodied in law to give our profession a boost into the real world where it can best serve the commonweal.

JEOFFRY B. GORDON, MD, MPH
*4747 Mission Blvd, Suite 4*
*San Diego, CA 92109*

REFERENCES

1. Cooke M: Physician risk and responsibility in the HIV epidemic (Medical Staff Conference). West J Med 1990; 152:57-61
2. Kardos GG: Who are you? West J Med 1990; 152:95-96

## Zinc

To the Editor: I read with great interest the article on zinc abuse in the February issue.[1] Since I was involved in the original studies of zinc deficiency, I would like to describe the conditions of zinc deficiency as found in humans and the consequences of using zinc as a supplement in multivitamins in the United States.

In 1961 Prassad and colleagues described a number of dwarfs in Iran who had geophagia and exhibited severe anemia and hepatosplenomegaly.[2] From the accumulated literature on studies in animals, they postulated that this could be due to zinc deficiency. Sure enough, after more extensive studies in Egypt and Iran, a number of people having malabsorption, possessing bizarre appetites, or using abnormal substances in their diet were found to suffer from a lowering of levels of zinc, which had affected their growth and sexual maturation.[3-5] During the 1970s, we studied a group of dwarfs in Shiraz using a double-blind controlled method that proved beyond any shadow of a doubt that zinc can alleviate hypogonadism and dwarfism in those who have been suffering from severe malnutrition.[5]

A number of other studies were done that showed that zinc deficiency may appear during stressful conditions such as surgical procedures and pregnancy.[6,7] In 1973 the World Health Organization published a blueprint for future use of zinc in nutrition.[8] To my knowledge, no change has been made since that expert committee meeting. In 1987 I described the nutritional value of zinc and clinical manifestation of zinc deficiency.[9]

It is unfortunate that some pharmaceutical companies have abused the facts regarding zinc deficiency in humans. A large number of products containing zinc have been manufactured and are being highly advertised as a potential remedy for a variety of conditions. I feel this is false advertising. Certainly, zinc deficiency occurs where there is an extreme degree of malnutrition or a situation of stress, at which time the body needs more trace elements and vitamins of all sorts. Some pharmaceutical companies have, however, in their advertisements, attempted to define zinc's nutritional value as being "better than gold."

In my opinion, the Food and Drug Administration must not only monitor the manufacturing of superfluous zinc products but must also stop misleading advertisements advocating their use. I think that zinc as a nutritional supplement should not be abused to the degree that it has been over the past few years, and I fully support Dr Forman, who indicated in his article that the dosage of 50 mg should be reduced to 5 mg. Finally, I also think that zinc should be sold only as a prescription item.

H. A. RONAGHY, MD
*Adjunct Professor*
*Div of International Health and Cross-Cultural Medicine*
*Dept of Community and Family Medicine*
*University of California, San Diego, School of Medicine*
*La Jolla, CA 92093*

REFERENCES

1. Forman WB, Sheehan D, Cappelli S, et al: Zinc abuse—An unsuspected cause of sideroblastic anemia. West J Med 1990; 152:190-192
2. Prasad AS, Halsted JA, Nadimi M: Syndrome of iron deficiency anemia, hepatosplenomegaly, hypogonadism, dwarfism and geophagia. Am J Med 1961; 31:352
3. Prasad AS, Miale A Jr, Farid Z, et al: Biochemical studies on dwarfism, hypogonadism and anemia. Arch Intern Med 1963; 111:407
4. Ronaghy HA, Caughey JE, Halsted JA: A study of growth in Iranian village children. Am J Clin Nutr 1968; 21:488-494
5. Halsted JA, Ronaghy HA, Abadi P, et al: Zinc deficiency in man: The Shiraz experiment. Am J Med 1972; 53:277-284
6. Kahn AM, Gordon HE: Alterations of zinc metabolism following surgical operation. Surg Gynec Obstet 1969; 128:88-90
7. Hambidge KM, Krebs NF, Jacobs MA, et al: Zinc nutritional status during pregnancy: A longitudinal study. Am J Clin Nutr 1983; 3:429-442
8. World Health Organization: Expert committee meeting on trace elements in human nutrition. Geneva, 1973
9. Ronaghy HA: The role of zinc in human nutrition. World Review Nutr Diet 1987; 54:237-254

## Confidential and Anonymous Testing

To the Editor: The letter to the editor by Hoffman and colleagues in the January issue[1] may mislead readers. The report compares the response to human immunodeficiency virus (HIV) antibody testing in Colorado and Oregon. The report states that in Colorado "All testing is done confidentially." Colorado, however, does not require proof of identification for testing.[2] Therefore, this system operates partially as an anonymous testing program. The Colorado testing program would be more accurately described as a hybrid system of confidential name reporting and optional anonymous reporting.

The authors' conclusion would be more accurately stated: *The comparison of testing in the two states does not support the contention that substantially fewer gay men are tested under the Colorado model of confidential and optional anonymous reporting.*

This distinction is particularly important because many argue that data from Colorado support the efficacy of mandatory name reporting programs. The Colorado data should only be interpreted to support or disprove the value of similar confidential and anonymous reporting models. They do not support or disprove the value of a dissimilar model, such as strict mandatory name reporting. Several studies suggest,

however, that mandatory name reporting would discourage substantial numbers of persons from being tested.[3-9]

The authors correctly caution about overinterpreting testing data, and they cite factors that should be considered in comparing testing programs and data from different states. In addition, I would add at least two other notable factors. These are (1) differences in state laws that protect HIV-infected persons from discrimination and (2) differences in the perception of the trustworthiness of the local or state health departments.

It would be valuable to have data from Colorado that specifically look at the extent to which the Colorado model encourages or discourages various populations within Colorado from being tested. Such studies may be difficult to conduct, but they ultimately would be more important than relying on testing curves between states in which many variables come into play.

JAMES P. KRAJESKI, MD
*2001 Union St*
*San Francisco, CA 94123*

REFERENCES

1. Hoffman RE, Wolf FC, Wood RC, et al: Confidential versus anonymous human immunodeficiency virus antibody testing (Correspondence). West J Med 1990; 152:75

2. Judson FN, Vernon TM Jr: The impact of AIDS on state and local health departments: Issues and a few answers. Am J Public Health 1988; 78:387-393

3. Fehrs LJ, Fleming D, Foster LR, et al: Trial of anonymous versus confidential human immunodeficiency virus testing. Lancet 1988; 2:379-382

4. Fordyce EJ, Sambula S, Stoneburner R: Mandatory reporting of human immunodeficiency virus testing would deter blacks and Hispanics from being tested (Correspondence). JAMA 1989; 262:349

5. Johnson WD, Sy FS, Jackson KL: The impact of mandatory reporting on HIV seropositive persons in South Carolina. Presented at the 4th International Conference on AIDS, Stockholm, 1988

6. Kegeles SM, Coates TJ, Lo B, et al: Mandatory reporting of HIV testing would deter men from being tested. JAMA 1989; 261:1275-1276

7. Lo B, Meacham S, Milliken N: AIDS screening: Who is willing to be tested? Presented at the 4th International Conference on AIDS, Stockholm, 1988

8. Moulton JM, Havassy BE: Evaluation of the San Francisco AIDS antibody alternative test site (Preliminary report submitted to the San Francisco Department of Public Health and the Centers for Disease Control, July 1987 (Revised October 1987)

9. Ohi G, Hasegawa T, Hirano W, et al: Change in acceptance rate for HIV testing when AIDS is notifiable. Presented at the 4th International Conference on AIDS, Stockholm, 1988

# Low-Birth-Weight Effects of Demographic and Socioeconomic Variables and Prenatal Care in Pima County, Arizona

IVY L. SCHWARTZ, MD, *Tucson*

*Low birth weight is the major determinant of infant mortality. Continuing declines in infant mortality in the United States are due to the use of neonatal intensive care services; less progress has been made toward preventing low birth weight. I examined how the demographic, socioeconomic, and health services use variables affected rates of low birth weights in Pima County, Arizona, in 1985. Women at greatest risk of having the smallest infants were those younger than 21 years and those with fewer than 6 prenatal visits. Nulliparous women with fewer than 6 prenatal visits showed a still greater risk of having an infant of low birth weight. Women without medical insurance coverage had babies with the lowest mean birth weights, as well as significantly fewer prenatal visits. As the number of uninsured in the United States increases, the effect of lack of insurance among pregnant women becomes increasingly important. To prevent low-weight births, comprehensive maternity care services must be available to all pregnant women regardless of ability to pay.*

(Schwartz IL: Low-birth-weight effects of demographic and socioeconomic variables and prenatal care in Pima County, Arizona. West J Med 1990 Jun; 152:725-728)

Infant mortality is considered to be a prime indicator of the health status of a nation and of the quality and availability of health services provided to its people.[1] The infant mortality rate of the United States is 10 deaths per 1,000 live births. There are 17 countries with lower rates than the United States. The lowest rates are found in Norway, Switzerland, Sweden, Finland, and Japan, with the lowest rate—5 deaths per 1,000 live births.[1]

The US infant mortality rate varies widely within racial groups. The rate for African-American infants is twice that of white infants, as is the rate of low-weight births.[2]

Low birth weight—2,500 grams or less—is the major determinant of infant mortality.[3] Two thirds of all infant deaths occur during the neonatal period; a third are postneonatal. Infants with low birth weights have a 40-fold increase in the risk of neonatal death over normal birth weight infants, and infants with very low birth weights—1,500 grams or less—have a 200-fold greater risk of death. Low birth weights contribute to postneonatal mortality as well, although to a lesser degree.

Other factors influence infant survival, including gestational age, race, maternal age, low maternal educational attainment, the use of various drugs, and previous poor birth outcome. Many of these exert their influence through a low birth weight, however.[3]

A low birth weight contributes to morbidity as well. Neurodevelopmental problems, congenital anomalies, and lower respiratory tract problems are more common, resulting in more frequent hospital admissions and outpatient visits for these infants. The financial burden is considerable: the average cost of neonatal intensive care is $12,000 per admission,[4] or nearly ten times the cost of uncomplicated maternal care services, including normal vaginal delivery in a hospital. The American Academy of Pediatrics has calculated that from $2 to $10 are saved for every dollar spent on prenatal care.[5] The social costs incurred by these infants and their families are substantial, as well.

Continuing declines in infant mortality rates in the United States are primarily due to declines in neonatal mortality rates through the increased use of neonatal intensive care. This has occurred during a period of only modest decreases in the rate of low-weight births.[6] There is ample evidence, however, that comprehensive prenatal care services are associated with a lower incidence of low birth weight.[6]

Local data defining the risk factors and evaluating strategies for preventing low birth weights are vital to the efforts of health policy makers to improve maternal and child health. I report the results of a study of the risk factors for low birth weight in Pima County, Arizona.

## Patients and Methods

Birth records for all low-weight births—2,500 grams or less—from July 1 to December 31, 1985, the most recent year for which complete data were available, of residents of Pima County, Arizona, were examined. Data obtained included maternal age, educational level, marital status, race or ethnicity, parity, census tract of the mother's residence, place of delivery, gestational age at first visit, total number of prenatal visits, and birth weight of the infant.

Pay source information was obtained from hospital and

From the Department of Family and Community Medicine, Section of Preventive Medicine, University of Arizona College of Medicine, Tucson.

Reprint requests to Ivy L. Schwartz, MD, Department of Family and Community Medicine, Section of Preventive Medicine, University of Arizona College of Medicine, Tucson, AZ 85724.

birth center records.* Pay source categories are as follows:

- *Insurance* includes those women with commercial coverage, including indemnity plans, health maintenance organizations, and those insured through the Civilian Health and Medical Program for the Uniformed Services, the federally sponsored insurance program for military personnel and their families;
- *Government* represents sliding-fee-scale programs partially funded by the state or federal government for low-income women who do not meet the strict eligibility requirements for the Arizona Health Care Cost Containment System (AHCCCS) enrollment;
- *AHCCCS* is the Arizona Medicaid program; and
- *Self-pay* refers to those without medical insurance paying fees for services.

The economic characteristics of the census tract of the residences of the pregnant women in the study were used to assess the influence of income on low birth weights. This was necessary as actual household income data are not available from birth records or hospital or birthing center medical records.

For purposes of statistical analysis, the number of prenatal visits was dichotomized into those women receiving 0 to 5 visits and those receiving 6 or more visits, defined as "adequate care."[7] In this way, the confounding effect of premature delivery on the relationship between low birth weight and extent of prenatal care could be minimized. That is, a woman initiating care at 8 weeks' gestation, for example, and obtaining prenatal care at appropriate monthly intervals would be correctly classified as receiving "adequate care" despite a premature delivery as early as 28 weeks of gestation.

During this six-month period, there were 324 live low-weight births. Multiple births were excluded because of their confounding effect on the birth weight, leaving 290 singleton births for analysis.

In some cases, data from all low-weight births in 1985—January through December—were available; when possible, these data were used in place of the six-month sample to provide a larger sample for analysis.

These data were compared with computerized summary data from the Pima County Health Department birth records for all births in 1985, using a one-sample $z$ test or $\chi^2$ as indicated.

The second portion of the data analysis was an analysis of variance in birth weight in the six-month low-birth-weight group, using the Statistical Package for the Social Sciences (SPSS) PC software.

## Results

The first set of data compares the low-weight group with the population of births in Pima County—that is, all weights.

While African-Americans contribute 4.6% of all births in Pima County, they account for 10.6% of all low-weight births ($z = 3.0$, $P < .01$). This represents a low-birth-weight rate of 14.3%, compared with an overall Pima County rate of 6.3%. Unmarried women produce 34.1% of low-weight births compared with 22.9% of all births ($z = 2.67$, $P < .01$). Women 20 to 34 years of age produce 77% of low-weight births compared with 81% of all births ($z = 2.16$, $P < .05$). Similarly, women younger than 20 years are over-represented in the low-weight group, although this did not reach statistical significance ($z = 1.55$, $P > .05$).

Significantly fewer women giving birth to low-weight infants had attained at least a high school education compared with all women giving birth (67.5% and 76%, respectively, $z = 2.79$, $P < .01$). Finally, although there is no significant difference in birth weight by timing of first prenatal visit, there is a significant association between birth weight and number of prenatal visits: 22.7% of women with low-weight infants had fewer than 6 visits, compared with 11% of all women giving birth ($z = 2.0$, $P < .01$).

The next set of data presents the results of the ANOVA in birth weight in the six-month sample of low-weight births (n = 290). Maternal age ($F = 3.9$, $P < .01$) and number of prenatal visits ($F = 16.0$, $P < .001$) are highly related to the severity of low-weight births. Figure 1 illustrates this relationship. Infants with the lowest mean birth weights were delivered of mothers 13 to 20 years of age and those with fewer than six prenatal visits. Although women with no prenatal care (n = 13) have infants with a higher mean birth weight than the group with one to five visits, little prenatal care is highly predictive of low-birth-weight infants with or without including women without prenatal care in the analysis. The influence of the number of prenatal visits on mean birth weights is seen in all age groups except women 25 to 28 years of age. Figure 2 illustrates a significant interaction effect of the number of visits and parity on mean birth weights. Nulliparous women with few visits have the lowest weight births ($F = 2.1$, $P < .05$).

The last set of data describes pay source categories among women giving birth to low-weight infants, evaluating the risk of low birth weight, race or ethnicity, parity, marital status,

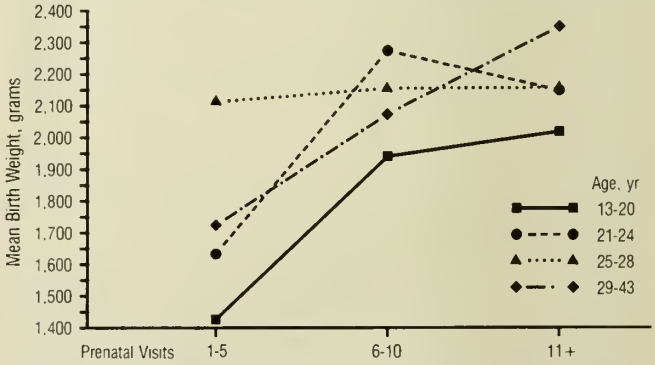



**Figure 1.**—The mean birth weight is plotted against maternal age and the number of prenatal visits among low-weight births. Women with no prenatal care are omitted (see text).

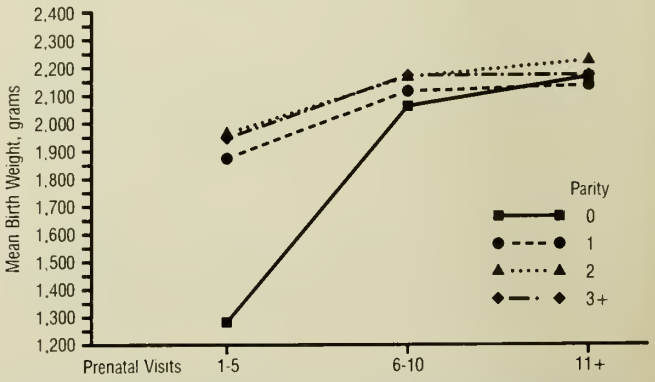



**Figure 2.**—The mean birth weight is plotted against the number of prenatal visits and parity among mothers having low-weight infants.

*The Pima County Health Department provided financial assistance and the following health care facilities cooperated in this study: Tucson Medical Center, University Medical Center, St Joseph's Hospital, Kino Community Hospital, Tucson General Hospital, Davis Monthan Hospital, and the Tucson Birth Center.

educational attainment, maternal age, income, and the number of prenatal visits. Women in the AHCCCS and self-pay categories have significantly higher proportions of low-weight births (7.6% and 6.5%, respectively) than women in the government and insurance groups (4.2% and 3.9%, respectively; $\chi^2 = 19.9$, $P < .001$). Similarly, among low-weight births, ANOVA reveals a trend toward a lower mean birth weight in the self-pay group, which reaches statistical significance when women of parity 3 or greater are excluded from the analysis (Figure 3, $F = 3.0$, $P < .04$). Mean birth weights among the other three pay source categories do not differ significantly from one another.

Among all women with low-weight births, 57.2% are white. Those with commercial insurance are disproportionately more likely to be white (67.9%) than women in the government group (54.5%), those without insurance (49.2%), and those with AHCCCS insurance coverage (42.4%) ($\chi^2 = 13.3$, $P < .004$). Although a $\chi^2$ could not be accurately calculated because of small expected frequencies in some cells, examination of the parity data reveals that women in the government and self-pay groups were more likely to be of parity 3 or greater and those with commercial insurance were less likely to be of parity 3 or greater. Overall, 68.1% of women birthing low-weight infants were married. Those with commercial insurance were most likely to be married (90.3%) compared with those in the government group (68.2%), those without insurance (63.9%), and those receiving AHCCCS services (22%) ($\chi^2 = 88.5$, $P < .0000$). Women with commercial insurance are more likely to have graduated from high school (87.3%) than women in the government group (59.1%), women without insurance (52.5%), and women with AHCCCS coverage (45.8%) ($\chi^2 = 44.3$, $P < .0000$). There was no significant difference in educational attainment among the last three pay source categories, and each was significantly different from the commercial insurance group. Although women in the insurance group were significantly older (mean age 26.5 years) than those in the other three pay source groups (government, 24.1 years; AHCCCS, 22.8 years; self-pay, 24.0 years), the age difference is small ($F = 8.1$, $P < .0001$).

The economic characteristics of the census tract of the residences of the women in the study are used as an income proxy to assess the influence of income on birth weight. In Figure 4, census tracts are divided into two groups: those in which 10% or more of the households had family incomes below the federal poverty level (representing 50% of Pima County census tracts), and those in which less than 10% of households were below the federal poverty level. Most pregnant women with commercial insurance lived in the more wealthy census tracts; the converse was true for women in the other three pay source categories. Finally, women in the self-pay group had the smallest mean number of prenatal visits (6.9), followed by the AHCCCS group (8.0), the government group (9.1), and the insurance group (9.6) ($F = 7.0$, $P < .0001$).

## Discussion

Women in Pima County at an increased risk of having infants with low birth weights included African Americans, those who have low educational attainment, are primigravidas, are not married, had little prenatal care, and either participated in the AHCCCS program or did not have health insurance. In addition, there was a trend toward an increased risk of low-birth-weight babies in women younger than 20 years. Previous studies have reported the relationship between young maternal age and low-weight births. The lack of a statistically significant result in this study is likely due to the small sample size of those women younger than 20 (n = 114). Among women bearing infants weighing 2,500 grams or less, significant factors included young maternal age, few prenatal visits, a lack of health insurance, and being primigravid. These data are consistent with those previously reported.[6]

The influence of income on the birth weight was evaluated through a proxy: the economic characteristics of the census tract of the residences of the pregnant women. Although an indirect measure of household income, the data strongly suggest that women without medical insurance share the socioeconomic characteristics of low-income women receiving government-funded or AHCCCS program services. The adverse effect of low socioeconomic status is likely due to the interplay of many factors influencing low birth weight. These data suggest that access to prenatal care ameliorates, in part, the influence of poverty on birth weights.

It was not possible to assess the underinsured in this study. Because almost all women will eventually present to the health care system for the delivery of their infants (if not before), however, the number of uninsured women not counted because they never sought care due to their inability to pay was minimized in this study. A sizable minority of

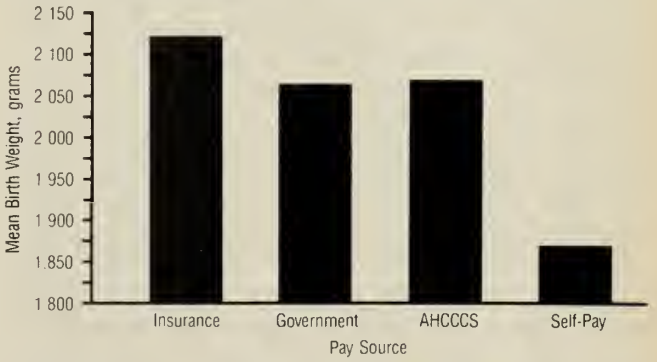



**Figure 3.**—The mean birth weight is plotted against the mother's pay source for perinatal care among low-weight births. AHCCCS = Arizona Health Care Cost Containment System

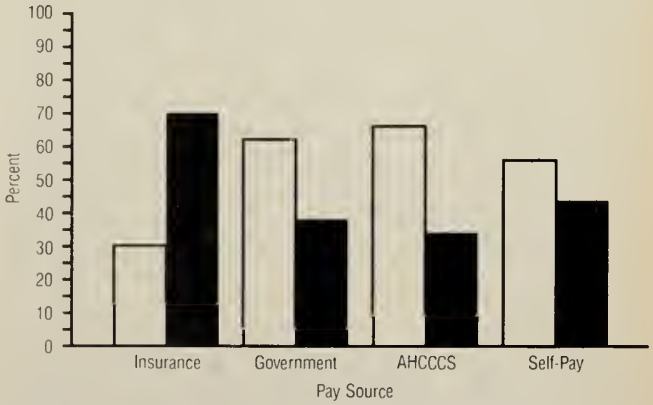



**Figure 4.**—A socioeconomic characteristic of the census tract of the mother's residence (income proxy) is plotted against pay source among low-weight births. □ = 10% or more of households are below the federal poverty level; ■ = less than 10% of households are below the federal policy level; AHCCCS = Arizona Health Care Cost Containment System

pregnant women in Pima County do not have medical insurance. These women are more likely to be women of color—African American, Hispanic, Native American, or Asian—to have completed less formal education, to have had three or more children, to live in poorer census tracts, to have had inadequate prenatal care, and to have higher rates of low-weight births. Uninsured pregnant women clearly represent a group at risk for poor perinatal outcomes. As the number of uninsured continues to grow in the United States, developing a mechanism for providing medical care services becomes increasingly critical.

Pregnant women receiving perinatal services through the AHCCCS program and those in the government sliding-fee-scale group would be expected to share a number of socioeconomic and other risk factors for low-birth-weight babies. Consequently, the differences found in the rate of low birth weights and the number of prenatal visits between these two groups are striking. Data from Arizona (Stephen Saunders, MD, Arizona Department of Health Services, unpublished data, 1987), California,[8] and elsewhere[9] indicate that case-managed comprehensive prenatal care yields lower rates of low birth weight than routine care and is cost-effective. The sliding-fee-scale programs in the government group in this study have features in common with case-managed care.

Although analysis of variance in birth weight through the entire range of birth weights could not be done owing to design constraints, it is instructive that the variables that exerted a significant influence on birth weights did so within the more narrow range of low-weight births. That is, maternal age, number of prenatal visits, parity, and pay source appear to define an increased risk for the lowest of low-weight birth.

Because of the uncertain quality of data on the duration of pregnancy from birth records,[10] the relative contribution of prematurity versus growth retardation to low birth weight could not be defined. This is extremely important in any analysis and plan of action to prevent low-weight births. One method to improve the accuracy of standardized records may be to provide data on gestational age as determined by the Dubowitz score on the newborn examination, in addition to the date of the last menstrual period.

Among low-weight births, only 18% of the variation in birth weights was explained. Other factors that could not be examined through a review of birth records and that may contribute to the risk of a low birth weight include cigarette smoking,[11,12] alcohol[11,12] and illegal drug use,[12] caffeine intake,[12,13] poor weight gain, battering,[14,15] and a number of variables that independently influence the occurrence of premature birth.[16] In addition, cultural and behavioral characteristics among differing racial, socioeconomic, and age groups may serve to enhance or deter healthy perinatal outcomes.[17] A more complete understanding of these behavioral and cultural factors will improve strategies to prevent low birth weights.

## Conclusions

Strategies to prevent low birth weight must address the unequal burden of low-weight births on economically and socially marginal Americans, including women living in poverty,[18] African-American women, pregnant teens, women with little formal education, and women without medical insurance.

It is clear from the AHCCCS data that simply providing a medical insurance card will not assure early and consistent prenatal care. Institutional barriers to care, such as unwieldy eligibility processes, should be defined and programs to eliminate these barriers instituted.[19] Similarly, language barriers, and racial or ethnic and socioeconomic class differences may impede the delivery of high-quality maternity care.[20] Future research should examine the influences of these variables on low birth weight and evaluate the efficacy of community-based interventions,[21,22] such as nurse home visitation programs,[23] media campaigns,[24] and the use of neighborhood health coordinators.[25,26]

Women without medical insurance constitute a group at high risk for poor perinatal outcomes. Further characterization of this group, including geographic mobility, income, and employment status, may help to define appropriate mechanisms for assuring access to care for these women.

Improving the health of women and children will require establishing a system of maternity care that is comprehensive, case-managed, culturally appropriate, and available to all women regardless of their ability to pay. This will go a long way toward preventing low-weight births and reducing infant mortality in the United States.

### REFERENCES


1. Grant J: The State of the World's Children, 1989—United Nations Children's Fund. New York, Oxford University Press, 1989
2. Shiono PH, Klebanoff MA, Graubard BI, et al: Birth weight among women of different ethnic groups. JAMA 1986; 255:48-52
3. McCormick MC: The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med 1985; 312:82-90
4. Fuchs VR, Perreault L: Expenditures for reproduction-related health care. JAMA 1986; 255:76-81
5. Child Health Financing Report. Evanston, Ill, American Academy of Pediatrics, Spring 1984
6. Institute of Medicine: Preventing Low Birth Weight. Washington, DC, National Academy Press, 1985
7. Donaldson PJ, Billy JO: The impact of prenatal care on birth weight—Evidence from an international data set. Med Care 1984; 22:177-188
8. Moore TR, Origel W, Key TC, et al: The perinatal and economic impact of prenatal care in a low-socioeconomic population. Am J Obstet Gynecol 1986; 154:29-33
9. Council on Maternal and Child Health, National Association for Public Health Policy: Background paper on universal maternity care. J Public Health Policy 1986; 7:105-123
10. David RJ: The quality and completeness of birthweight and gestational age data in computerized birth files. Am J Public Health 1980; 70:964-973
11. Shiono PH, Klebanoff MA, Rhoads GG: Smoking and drinking during pregnancy—Their effects on preterm birth. JAMA 1986; 255:82-84
12. Fried PA, O'Connell CM: A comparison of the effects of prenatal exposure to tobacco, alcohol, cannabis and caffeine on birth size and subsequent growth. Neurotoxicol Teratol 1987; 9:79-85
13. Martin TR, Backen MB: The association between low birth weight and caffeine consumption during pregnancy. Am J Epidemiol 1987; 126:813-821
14. Helton AS, McFarlane J, Anderson ET: Battered and pregnant: A prevalence study. Am J Public Health 1987; 77:1337-1339
15. Bullock L, McFarlane J: The birthweight/battering connection. Am J Nurs 1989; 89:1153-1155
16. Ernest JM, Michielutte R, Meis PJ, et al: Identification of women at high risk for preterm-low-birthweight births. Prev Med 1988; 17:60-72
17. Dowling PT, Fisher M: Maternal factors and low birthweight infants: A comparison of blacks with Mexican-Americans. J Fam Pract 1987; 25:153-158
18. Braveman P, Oliva G, Grisham Miller M, et al: Women without health insurance—Links between access, poverty, ethnicity, and health. *In* Women and Medicine (Special Issue). West J Med 1988; 149:708-711
19. Jones J: Overcoming barriers to Medicaid eligibility—Notes from the field. Am J Public Health 1986; 76:1247
20. Temkin-Greener H: Medicaid families under managed care—Anticipated behavior. Med Care 1986; 24:721-732
21. Institute of Medicine: Prenatal Care—Reaching Mothers, Reaching Infants. Washington, DC, National Academy Press, 1988
22. Sakala C: Community-based community-oriented maternity care. Am J Public Health 1989; 79:897-898
23. Olds DL, Henderson CR Jr, Tatelbaum R, et al: Improving the delivery of prenatal care and outcomes of pregnancy: A randomized trial of nurse home visitation. Pediatrics 1986; 77:16-28
24. Mahan C: Results of Florida's statewide efforts to reduce low birth weight. Perspect Prev 1988; 2:24-30
25. Freeborn DK, Mullooly JP, Colombo TJ, et al: The effect of outreach workers' services on the medical care utilized by a disadvantaged population. J Community Health 1978; 3:306-320
26. Colombo TJ, Freeborn DK, Mullooly JP, et al: The effect of outreach workers' educational efforts on disadvantaged preschool children's use of preventive services. Am J Public Health 1979; 69:465-468

# Trench Foot—A Study in Military-Medical Responsiveness in the Great War, 1914-1918

JOHN S. HALLER, Jr, *Denver*

*Along the nearly 15,000 miles of trenches on the western front in the Great War of 1914-1918, a condition known as "trench foot" caused serious attrition among the fighting troops and resulted in swollen limbs, impaired sensory nerves, inflammation, and even loss of tissue through gangrene. Physicians, sanitarians, and military officers explored numerous theories regarding etiology and treatment before focusing on a combined regimen of common-sense hygiene and strict military discipline.*

(Haller JS Jr: Trench foot—A study in military-medical responsiveness in the Great War, 1914-1918. West J Med 1990 Jun; 152:729-733)

The Great War on the western front began as a war of movement. In early August 1914, German armies swept through Belgium, and by August 24, an extensive retreat of the Allied armies sent shock waves through the capitals of Europe. In September, however, the German advance halted with the battle of the Marne, which was quickly followed by a race to the sea (October 10 to November 10), with the German and French armies attempting unsuccessfully to outflank each other. By the end of the first battle of Ypres (October 30 to November 24), the western front had become fairly well fixed, confined largely to trench warfare, which endured for nearly four years.[1-3]

Eventually, more than 15,000 miles of trenches stretched in zigzag fashion from the North Sea to the borders of Switzerland and became the killing ground for soldiers on the western front. The battle lines between the belligerent powers settled into a stalemate in which opposing armies dug in like rabbits, living an almost subterranean life and fighting each other across a narrow "no-man's-land" in harrowing but futilely destructive encounters. For soldiers, the trench became home, the line of defense, and, unless kept dry with boards or lime to cover the trench bottom and walls, a veritable incubator for bacterially spread diseases and other incapacitating problems. Although troops in the Great War fared better in terms of general health than in any previous war in history, trench warfare introduced its own special diseases and characteristic war wounds. Besides trench fever, tetanus, head wounds and shell shock from artillery barrages, and gas gangrene, soldiers experienced an inordinately high rate of so-called frostbite or trench foot. Of all diseases grouped under the etiologic title "physical environment," frostbite and trench foot were of principal importance, causing serious attrition in the field armies. Because these maladies interfered with a soldier's ability to march, they also "became the touchstone of health discipline."[4(p90)]

## Early Days of War

Between October 25, 1914, and March 10, 1915, the war theatre experienced an unusually wet season, with only 18 days of dry weather. Rain became the implacable enemy of both armies, and the trenches, which then consisted of many natural ditches, flooded with water. Although the terrain varied considerably along the 475 miles of front, most soldiers found themselves living ankle deep in mud except for a few months in summer. And in the weeks after the first battle of Ypres, soldiers held an extended line for hours on hours in water and mud up to their waists or even their armpits.

The conditions of trench warfare included nervous strain and long hours of inactivity, with men remaining almost motionless and in cramped positions, immersed in mud or cold water at near-freezing temperatures. As the temperatures fell, those standing knee deep in ditches faced actual freezing, and field ambulances reported treating cases of frostbite. Even with improved weather conditions, physicians found themselves not treating actual frostbite but characteristics that were clinically indistinguishable from frostbite and which they initially called "chilled feet" or "trench foot."[5(p600)]

The typical medical history of trench foot began with soldiers feeling their feet becoming cold and then ultimately losing all feeling. Beyond the initial discomfort associated with cold feet, there was no other complaint until the feet swelled around the ankles, the swelling sometimes extending up the calves. At this stage, soldiers could not replace their boots once they had been removed. It was thus not unusual to see men in a battalion hobbling along in their bare feet or in boots that were too tight to lace. In moderate cases, the condition lasted two to three weeks, but the more severe cases lasted from six weeks to three months or more.[6(p1143)]

Among soldiers diagnosed with trench foot, many had worn their boots and puttees for periods from 72 hours to 14 days without taking them off. Often, boots that were large when dry had shrunk under the wetness. "Within a few minutes or even before entering the trenches for their spell of days and nights of fighting," wrote one medical observer, "the boots of the majority of my patients had been soaked, and so they remained until, on their removal, the gangrene or other manifestations were discovered."[7(p38)]

The field ambulance workers soon had on their hands men whose feet were not just swollen but showing color

From the Department of History, University of Colorado, and the Department of Preventive Medicine and Biometrics, University of Colorado Health Sciences Center, Denver. Reprint requests to John S. Haller, Jr, 7860 S Hudson, Littleton, CO 80122.

change, from bright pink blush to a dead, black gangrenous appearance. In some, the skin was covered with a bullous eruption. In almost all instances, the disabling effects resulted from exposure to water when the temperature was above the freezing point. Only a small number—less than 10%—suffered from classic frostbite or actual freezing of the tissues.[5(pp602-603)]

In the winter of 1914, S. Delepine, Professor of Public Health and Bacteriology and Director of the Public Health Laboratory at the University of Manchester, initiated a study of the effects on hands and feet immersed in water above or below the freezing point. He divided his experiments into two groups: those unprotected from wet cold and those for whom protection had been provided.[8(p176)]

From his clinical and experimental data, Delepine concluded that "neither exposure to a freezing temperature, nor congelation of the tissues are necessary factors in the production of the pathological state generally known by the name of frostbite." The severity of lesions in so-called frostbite was determined not only by the intensity and duration of the cold but by other predisposing factors including imperfect circulation, lack of exercise, water, and stress. The name frostbite suggested "a destructive lesion due to the action of frost," but Delepine considered the term unsatisfactory from a scientific point of view and found most of the alternative names equally unsuitable. Although the word trench foot became the choice of European physicians—the Americans continued to use the term frostbite—this term, along with "water bite," "chilled foot," and "boot bite," failed to meet the needs of scientific nomenclature. Instead, Delepine proposed the term "frigorism," which he defined as a state of the body "produced when the cooling of the body or any part of it is progressive—that is, when it cannot be compensated by the production in the tissues, and the distribution by the circulating blood, of a sufficient amount of heat." When the cooling of a body extremity reached a certain critical point, the natural functions of the tissues stopped and freezing occurred, thus creating additional complications that affected the actual state of the cells and fluids.[8(pp173-174),9(p888)]

In studies undertaken by the British Medical Department, physicians not surprisingly found that the instances of trench foot coincided with cold and wet weather. Of interest, however, the highest number of cases occurred during October and November, falling off in December and January during the freezing weather and rising again after the thaw. During the first year of the war, one battalion lost 400 men in two days to trench foot, and many of these men suffered subsequent amputations. Physicians treating these cases soon began dividing them into three different groups: The first type they characterized as functional anesthesia with impairment of movement; a second type showed slight edema, functional anesthesia, and impairment of movement; the third type exhibited well-marked edema, bleb formation, and ecchymoses.[5(p598)]

## Pathology and Etiology

The etiology of trench foot remained confused through most of the war years. While some medical authorities expressed the opinion that the condition derived from actual freezing of the tissues, others attributed it to the loss of vitality in the limbs resulting from water soaking into the tissues. Still others pointed to a fungus or mold found in soil, straw, and manure that entered through lesions in the feet. One enthusiastic writer even ascribed trench foot to "the leaking, through wet feet, of the electrical energy manufactured by the central nervous system." To correct this disorder, he proposed the use of "dielectric oil." Despite the different approaches, all agreed that trench foot thrived best at low temperatures and high moisture.[5(p601)]

In instances of classic frostbite, the skin tended to swell after thawing, becoming red and covered with blisters. Later, portions of the skin or deeper tissue died and separated as a dry gangrenous mass. In these cases, the amount of tissue lost depended in large measure on the duration of cold and the temperature reached inside the tissues. During the thawing process, patients experienced intense pain, followed by tingling and itching of the affected parts. Any healing was complicated by swollen tissue cells, impaired sensory nerves, and inflammation.[7(p36)]

In situations not involving actual freezing of the parts but, rather, long exposure to cold and dampness, the effects were to be seen in the vascular and lymphatic systems. Minor chilling of the exposed superficial parts affected the smaller arteries and later the larger and deeper arteries, resulting in a vasoconstriction in the extremities. When this occurred, a soldier experienced pain from the effects of cold on the nerve endings, and the body movements became hindered. Eventually, vasodilation followed vasoconstriction, and the parts became red and erythematous or blue, vivid, cyanotic, and congested. Over time, continued exposure to wet and cold caused the skin to blister and ulcerate, with a tendency to infection and loss of tissue through gangrene. German writers identified this condition as frost gangrene in the absence of frost.[7(p37),10]

Early in their classification of types, physicians voiced the opinion that imperfect circulation brought on by surface chill, general muscular inactivity, and tight-fitting boots were the principal pathogenic factors in the establishment of trench foot. Helpful in this analysis were the ample data available as physicians and sanitary personnel examined hundreds of soldiers of the same relative age and health, who were wearing the same types of boots, socks, and puttees, and who had been standing in freezing mud or water for hours at a time. Their examinations of these men provided a consistent level of data enabling them to generalize the early symptoms of numbness, functional anesthesia, and swelling.[8]

The similar pathologic features of trench foot with those of Raynaud's disease did not go unnoticed. Two varieties of the disease, the blue congested and the white, were reproduced almost exactly among soldiers in the trenches. Of the two, the blue congested form predominated, but a certain number also evidenced the "dead white foot." Both suggested an underlying vasomotor condition. "I have admitted cases in which the feet were white, numb and shrunken, and which shortly afterwards were found to be swollen and blue," remarked one observer. "This would suggest that the condition, commencing as a vasomotor constriction, passes on to vasomotor paresis and paralysis, with damage of the capillary walls, and consequent hemostasis, exudation and finally gangrene."[5(p600),11(p664)]

Early efforts to substantiate a bacterial cause of trench foot indicated that a bacterial invasion resulted from lowered vitality of the foot from cold. This thesis, put forward by Gordon Watson and others, found its greatest acceptance with the French medical community, which attributed the

condition to a fungoid infection of the epidermis and the subsequent invasion of the devitalized dermis by mycelium. Advocates of the thesis suggested that the bacterial invasion was not the first cause of the condition but rather a secondary one. The growths obtained by culture were of organisms present in mud that became pathogenic in devitalized tissues. French scientists claimed to have isolated from the gallbladders of patients who died an organism called a "mycosis" that, when inoculated into rabbits, produced skin lesions resembling trench foot. The Inspector General of the French Army issued a general circular noting a microbic origin, the agents of which were isolated from trench mud. Experiments on animals reproduced various symptoms associated with trench foot, suggesting that the disease was similar to mycetoma, the fungus foot of Madura that English surgeons had named "tuberculous foot."[5(p601),6(p1143),11(p665)] To prevent this, physicians recommended painting the feet with formalin, using a dusting powder composed of French chalk and zinc oxide, and supplying a generous diet of foods containing nitrogen.[12]

From October to the end of December 1915, Captain Basil Hughes of the Royal Army Medical Corps was attached to a regiment holding a section of the line where the conditions of trench fighting were exceedingly poor. The cases that Hughes studied were almost always identical. During this period, the troops were constantly exposed to rain and, unable to move about, either stood or crouched during the daytime hours and slept in a sitting position at night. He learned that while on duty, the men frequently complained of numbness and a "pins and needles" sensation in the feet. On coming off duty, their feet swelled and were red and tender to touch.[13,14(p298)]

On investigation, Hughes discovered that while the shoes worn by troops were typically a size larger than normally required and socks were frequently changed, the boots nevertheless filled with a "thick soupy mud" that had come in contact with decomposing organic matter. This, he theorized, was the exciter of the condition found in so many of the men. In testing his thesis, Hughes directed soldiers to rub grease and whale oil into their feet, wear clean dry socks, increase their exercise, and wear rubber knee boots when in the trenches. Although the boots prevented the men from coming in direct contact with the mud, Hughes found to his surprise that the incidence of trench foot did not subside. From this evidence, he concluded that the bacteria in the mud were not a factor in trench foot.[13]

An inquiring scientist, Hughes then searched for answers other than a microbic cause. He next considered fatigue and the "consequent collection of waste products of metabolism in the cellular tissues of the lower extremities," thinking that this could be the predisposing cause while cold and wetness acted as the exciters. Accordingly, he ordered hot soup made with fresh meat and vegetables sent to the trenches each night. At the same time, Hughes continued to require the men to wear rubber boots to protect their feet from mud. Socks, however, still got wet from boot condensation. In testing his new thesis, Hughes discovered that the incidence of trench foot declined, and he attributed the change to improved rations.[13]

Still Hughes was not satisfied. On checking other trench lines during the winter of 1915, Hughes found the saps, firebays, traverses, and communication trenches deep and in good condition, with sufficient width to allow men to move about. In making his rounds, however, he noticed that men who sat on the fire-step with their legs hanging down experienced a sensation of numbness and "pins and needles" in their feet and legs. After learning that the experience was a common one, he insisted that the men rest with their feet on the fire-step rather than hanging over it. During the period when these precautions were taken, no incidence of trench foot was reported. Hughes concluded from his observations and actions that two factors produced trench foot. The predisposing factor was fatigue but the exciting factor was purely mechanical, namely, "venous stagnation and consequent exudation of material into the tissues of the foot." Accordingly, he insisted that men in the trenches rest with their legs elevated, that they use blankets when resting on the fire-step, that they change socks frequently, and that they take hot soup and rum to keep up vitality.[13(p713)]

**353. Frostbite—Precautions**

Cold is likely to give rise to frostbite when the circulation of blood is interfered with or rendered feeble. The feet are likely to be frostbitten under the following circumstances:

1. When boots and puttees are too tight
2. When the general circulation throughout the body is less active than normal
3. When the socks, boots, and puttees are wet.

The best precautions are on the following lines:

1. Boots should not fit tightly but should be at least a size too large. When large boots are worn it is well to wear two pair of socks, but this is dangerous if the boots are small, as it leads to further pressure on the foot. Puttees should never be applied tightly.
2. The general circulation can be kept up by keeping the body warm and dry. A mackintosh sheet worn over the greatcoat is of assistance where no waterproof is available.
3. A dry pair of socks should be carried in the pockets when available. Officers should see that dry standing is provided in the trenches whenever possible by means of drainage, raising of the foot-level by fascines of brushwood or straw with boards on top, or by the use of pumps where these are available.

**Figure 1.**—The British Army issued these precautions for the prevention of frostbite (from Delepine[8(p175)]).

## Prophylaxis

In response to the high incidence of frostbite and trench foot, the British Army issued Army Routine Orders, dated November 23, 1914, outlining steps to prevent frostbite (Figure 1).

Ideally, dry weather and good drainage in the trenches eliminated the problem of trench foot. Such an environment, however, seldom prevailed under battle conditions. Constant bombardment and the need for readiness often precluded efforts to pump out saps, fire-bays, traverses, and communicating trenches. The military initiated efforts to drain the trenches and provide them with boards—known as "duckboards"—placed at the base of the trench. By 1915, miles of duckboards were laid in the trenches, many of which either floated away with the heavy rains or were trodden into the mud.[5]

More effective prophylaxis involved thorough foot and boot inspection of soldiers before they entered the trenches, the systematic use of soap, water, and "French powder" (borated talc and camphor), oiling the feet, and insisting that boots be well greased and of ample size so as to ease pressure on the feet when wet. Additional precautions included loose-lacing of the boots as well as loose-binding of the puttees to

ensure adequate circulation. Physicians were quick to point out the problems of puttees; when wet, they constricted circulation to the legs and tended, in cold weather, to freeze. Other measures included wearing clean dry socks, filling the boots with hot bran or hot crumpled newspapers to absorb water, exercising whenever possible (in some instances, soldiers lay down on a tarpaulin in the trenches and did overhead feet exercises), even if it only meant stamping their feet or moving their toes within the boots, and placing dry sandbags over the feet or securing bags stuffed with straw around the legs and feet.[5,11,15] Finally, Hampstead Hospital, which initiated some of the earliest studies of classic frostbite and trench foot, recommended the liberal use of salted lard, which protected the feet against water and also acted as an antiseptic.[16(pp635,640)]

In situations where soldiers had little time to check each of these items, they often simply poured oil of mustard into the top of their boots because it conveyed the sensation of heat to the feet. Whale oil was another popular prophylaxis within the British and Australian armies. Those battalions whose incidence of trench foot was lowest attributed their success to both the whale oil and the general measures that were enforced around its use, such as frequent removal of boots and socks, careful supervision by officers, and using friction and rubbing, which helped circulation.[4(p100)]

Gum boots with india rubber extensions and waders were available to the British Army in 1915 and 1916 and distributed on a scale of 2,500 per division. Nevertheless, many in the military considered them too cumbersome and expensive for widespread use. Moreover, during periods of marching, the legs and feet perspired profusely, subjecting them to the very conditions that the boots were intended to avoid. The solution, as some officers were to discover, was to put on the gum boots *after* arriving at the trenches to avoid the risk of their becoming wet from condensed perspiration.[14(pp296-297)]

Others turned to alternative methods such as adopting Labradorian footgear consisting of two or three layers of watertight skins. Within certain British lines, soldiers wore boots large enough to permit the wearing of at least three pairs of socks—an inner, light pair soaked in a salted ointment and two heavy woolen outer pairs dipped in paraffin.[17] Major Grenfell's experiments in Labrador and Newfoundland over a 25-year period showed the effectiveness of layered clothing that permitted the body to breathe through the garments. Grenfell opposed the use of india rubber boots or other waterproof garments because they held moisture when the body exercised.[8]

Another alternative involved the use of thin oil-silk fabric waterproofed by oxidized linseed oil. Experiments on the permeability of oil-silk of various thicknesses and with the addition of resins, neutral fats, and paraffin wax resulted in a preference for linseed oil boiled with a lead salt.[9] The use of oil-silk bags involved the wearing of a dry woolen sock, as thick as possible but not tight fitting, drawn over the dry and warm foot powdered with French chalk. An oil-silk or "anti-frigor" bag, as it was sometimes called, was stretched over the sock, followed by a second sock that was not thick but sufficiently large. A soldier then wore boots at least two sizes larger than his regular foot size.[5]

## Treatment

When local freezing occurred, physicians first used friction with snow or cold water rather than immediately inducing warming. Friction with turpentine and oil or spirits and soap liniment was also used in the early stages of treatment, followed by maintaining the affected parts in a dry, warm, and aseptic environment. In situations not involving actual freezing, physicians typically wrapped the limbs in wool, kept them in a raised position, and powdered them with a dusting material such as zinc oxide, boric acid, and iodoform, or painted them with a 2% solution of iodine. In addition, physicians encouraged active movement of the feet and legs to increase vascularity to the feet and recommended massage, mild applications of hot air, and treatment with static electricity.[7(p49)]

As the cause changed, physicians turned to internal doses of potassium iodide and the external use of tincture of iodine and salvarsan—methylene blue. Wet dressings soaked in borated camphor solution worked better than dry dressings. Raymond and Parisot claimed success by washing the feet with warm water and a mixture of green soap, camphor, and borate of soda.[18] This was followed by carefully drying and covering the feet with a layer of absorbent cotton soaked in a solution of camphor and borate of soda. The area was then covered with oiled silk or a rubber sheet, with the dressings changed each day. In addition, because tetanus occurred frequently, physicians administered antitetanic serum to all patients. With the vesicular form of trench foot, physicians recommended denuding the area of its gelatinous character and covering it with compresses soaked with camphor in ether. In the worst cases, surgeons removed the purulent layer or fetid edema fluid, washed the area thoroughly with antiseptic solution, then applied camphorated ether. Surgeons preferred amputating at a healthy point beyond the infected area. The most frequent complication was tetanus, while gas gangrene was also prominent.[6]

## Retrospect

Although the prophylactic measures undertaken by physicians on both sides of the trenches improved measurably the health of the soldier and reduced the incidence of trench foot, the military eventually realized that much of the problem derived from hygienic negligence among officers and men or, as Macpherson noted in the official documents of the Great War, the failure of "making . . . a fine art of the 'toilet' of the feet."[14(p295)]

Eventually, officers across the western front developed elaborate organizational arrangements to ensure fresh supplies of socks to men in the trenches. Waterproof bags full of clean dry socks were sent every night to the trenches along with the rations. This enabled every soldier to receive a fresh pair of socks every 24 hours. To maintain circulation and avoid any form of constriction of the feet and legs, officers prohibited the wearing of puttees in the trenches and encouraged the men to move about as much as possible. Some even instituted a regular removal of the boots, followed by foot-rubbing drills and massage. Officers also insisted on correct posture when sitting on the fire-step or crouching against the wet side of a trench. Other changes included the rule that trench duty in a water-logged sector should not exceed 24 to 36 hours; the institution of "foot-washing centres"; a liberal ration of hot food in the trenches; removing boots and socks at least twice a day while in the trenches; the more extensive use of gum boots; and the gradual abandoning of greasy preparations for the use of dry foot powder. Nevertheless, British soldiers never completely gave up using their whale

oil. When in the line, a battalion received ten gallons of the oil as its daily issue.[14(pp299,480-481,484-486)]

Most important, the army placed the responsibility for the proper care of the men's feet on company and platoon officers rather than on the medical corps. The Fourth Army's Standing Order No. 595, issued June 20, 1917, stated that "CO's [company officers] will be reminded that the loss of effective strength due to the prevalence of this trouble is an indication of faulty discipline and faulty interior economy, and they will, therefore, be held responsible that the instructions laid down are carried out under the strictest supervision by company officers."[14(p482)] The real secret to preventing trench foot was perhaps best revealed in the comment of A. G. Butler in *The Australian Army Medical Services in the War of 1914-1918:* "The CO and all officers entered enthusiastically into the spirit of the game."[4(p100)] In other words, the successful elimination of trench foot as a major source of attrition turned out to be little more than good morale, common-sense hygiene, and strict military discipline.

## REFERENCES


1. Ashworth T: Trench Warfare 1914-1918: The Live and Let Live System. New York, Holmes & Meier, 1980
2. General Staff: Notes for Infantry Officers on Trench Warfare. London, HMSO, 1916
3. Winter D: Death's Men: Soldiers of the Great War. London, Allen Lane, 1978, pp 80-140
4. Butler AG: The Australian Army Medical Services in the War of 1914-1918, vol 3. Canberra, Australian War Memorial, 1940
5. Trench foot. Milit Surg 1917; 41:598-609
6. Sherwood-Dunn B: Trench-foot. Med Rec 1917; 91:1143-1146
7. Fearnsides EG, Cantab BC: Frost-bite. Br J Dermatol 1915; 27:33-51
8. Delepine S: Contribution to the study of the causes and prevention of 'trench-foot,' so-called. Int J Surg 1916; 29:173-179
9. Delepine S: Remarks on some of the effects of exposure to wet cold and their prevention. Br Med J 1915; 2:888-892
10. Kohler A: Ueber Frost-schaden ohne Frostwetter. Zentralb Chir 1913; 40:1363
11. Soltau B: Trench-feet. J R Army Med Corps 1916; 26:664-668
12. Blackman JG: Trench foot. Br Med J 1916; 1:818
13. Hughes B: The causes and prevention of trench foot. Br Med J 1916; 1:712-714
14. Macpherson WG: History of the Great War Based on Official Documents: Medical Services—Hygiene of the War, vol 2. London, HMSO, 1923
15. Hayden AD: Remarks on the condition known as trench foot. J R Army Med Corps 1917; 29:181-191
16. Waller W, Rideal EK: Report on 'trench foot.' J R Army Med Corps 1916; 26:635-641
17. Loew HK: A summary of medico-military facts developed by experiences on European battle fronts. NY Med J 1917; 115:5-10
18. Raymond U, Parisot J: Etiologie, prophylaxie, et thérapeutique de l'affection dite gelure des pieds. Compt rend Acad Sci (Paris) 1916; 167:694-696

# A Tribute to
# Malcolm S. M. Watts, MD

M CHRISTINE TORRINGTON

Editor
1968-1990

# Special Editorials

## A Tribute to MSMW

AFTER TWENTY-TWO YEARS, A VERY ABLE, THOUGHTFUL, AND WISE PHYSICIAN LAYS DOWN HIS EDITORIAL PEN.

MALCOLM WATTS, who for over 22 years has edited the official journal of the California Medical Association—*California Medicine* and subsequently *The Western Journal of Medicine*—retires as editor in the first half of 1990. He has done a remarkable job and brought *The Western Journal of Medicine*, which is now also the official journal of the medical associations of Arizona, Denver, Idaho, Nevada, New Mexico, Washington, Utah, and Wyoming, to the point where it is one of the best general medical journals published in this country. Far-ranging and yet practical, it is informative for physicians in practice and, at the same time, reflects much of what goes on in medicine in the West.

In a sense, Malcolm Watts had a perfect background to occupy an editorial chair. He had had extensive experience in the private practice of internal medicine in San Francisco, accumulated a substantial bibliography, developed a gradually growing and then prevailing interest in continuing medical education in an academic setting and in the California Medical Association, and a leavening experience in organized medicine as president of the San Francisco Medical Society and of the American Society of Internal Medicine. All of this experience was well salted with a wide interest and active participation in the "Role of Medicine in Society," with its broad implications and increasing importance in the ethical aspects of medicine.

The wisdom he has developed he has expressed very well in the editorials in *The Western Journal of Medicine* signed MSMW, and likewise he has shared it with the Scientific Board and the Council of the California Medical Association. Ably assisted in the academic and scientific fields by Holly Smith, the associate editor of *The Western Journal of Medicine* for the same 22 years, the team of Watts and Smith has made a very important contribution to the continuing medical education of the profession in the western United States and indeed throughout the country.

As we bid our editorial good-bye to Malcolm Watts, let us keep in mind how long and successfully he has carried out his editorial duties and how much he has done for the medical associations in the West. He has been a giant in medicine, and *The Western Journal of Medicine* will long stand as a monument to his efforts.

DWIGHT L. WILBUR, MD

IT IS A PRIVILEGE for me to have this chance to make a few comments about my close friend and long-term colleague, Mal Watts. I thought that I would start with a standard official delineation of his professional pedigree.

Mal is a New York Scot, as reflected in the nomenclature of his antecedents—Watts, Stuart, McNeal, Forbes. After attending Trinity School in New York, he scurried north to Harvard for both his undergraduate and his medical degrees, the latter in the auspicious year of 1941. After a year of internship at Bellevue Hospital (Cornell Service), he was caught up in World War II, entering the Army Medical Corps as a 1st Lieutenant but emerging as a Major. The war mobilized Mal from his Eastern habitat and revealed to him the splendors of California, whose praises had already been seductively sung by his classmate and friend, Herbert Moffitt. Clearly the lesson was heeded, for he promptly returned from Army duties to residency training at the University of California, San Francisco (UCSF), and soon after to marriage with Genevieve Moffitt. Fortunately for us, he has been sessile here ever since. The Good Book states that the "Wise men commeth from the East"—but clearly the object of their adoration lay in the West. It was similarly true for the wise Scot from the New York-Boston axis.

I shall not write of Mal's entering the practice of medicine with Dwight Wilbur, after the completion of his chief residency. It is interesting to note, however, that Mal's first three publications were co-authored with Dwight, who has been a lasting influence in his life. Mal continued in the private practice of internal medicine for almost 30 years, until his increasing responsibilities with the University of California obviated that time commitment. I cannot begin to summarize Mal's many contributions to UCSF, which started when he was a resident and which continue to this day. The university quickly recognized his gifts as a leader so that even in his early days of faculty membership, he was given major academic responsibilities in the Dean's Office—best described as "Dean For External Affairs." These external affairs he handled quietly and adroitly, as indeed he has everything else that comes his way. In 1983 he received the UCSF Medal, the highest honor that the University can bestow, in recognition of his signal contributions to health education, community health care, and public service. A few months ago Chancellor Julius R. Krevans and many of his university colleagues sponsored a special dinner for Mal and his family in further recognition of his invaluable academic legacy.

The university has had to share Mal, however, with many other entities. To list a few, he has been president of the San Francisco Medical Society, of the American Society of Internal Medicine, and of the Alliance for Continuing Medical Education. On a more bibulous theme, it should be noted that he has also been president of the Society of Medical Friends of Wine. I shall not attempt to summarize his many other contributions to this community, to the state, and to the nation.

In this issue we are celebrating only one phase of Mal's multifaceted life—his editorship since 1968 of this medical journal, a stretch of more than 22 years. In some ways that seems a short period of time, because I have shared those years with him and, like all good things, they have seemed to whistle by all too quickly. On the other hand, we can say that Mal has been editor for more than 10% of the duration of our nation! But longevity, although noteworthy, is not what we celebrate. We are celebrating high achievements and the exceptional personal attributes that underlie them. Under his leadership this journal has improved remarkably, both before and after its transmogrification in 1974 from *California Medicine* to the more spacious scope of *The Western Journal of Medicine*. These changes are a matter of public record. I would rather comment briefly on style. Good fun and a sense of high adventure have always fueled our editorial meetings rather than the sober lash of requisite responsibilities. Remarkably, much was accomplished with convivial give-and-take around a noontime table at Trader Vic's, although I should probably not reveal this departure from austerity to our financial overlords. Although Mal always carried the ultimate responsibility, his openness allowed all of his associates, of which I was privileged to be one, a keen and exhilarating sense of participation.

Among the many other new ideas that Mal brought to the journal was that of the Epitomes, pithy summaries of various advances in medicine. Unfortunately, I cannot capture the essence of Mal Watts in this verbal Epitome. But of the many words that come to mind the one that seems most appropriate is integrity—intellectual integrity in his approach to his profession and to the problems that lie on the interface between medicine and society; personal integrity in his interactions with others in all walks of life. The Greek conception of happiness was: "The exercise of vital powers along lines of excellence in a life affording them scope." In this issue we salute a man who has exercised those vital powers superbly well and whose own life has uniquely encompassed that scope. Fortunately for Linda Clever and me, Mal will remain as a honored colleague with *The Western Journal of Medicine*. More important, he will remain, as he has always been, a distinguished physician, a wise counselor, and a warm friend.

At the journal we were very concerned about finding a suitable gift to mark the official end of Mal's distinguished editorship. We finally decided to give him a uniquely valuable gift—to return to him the tangible essence of his own wisdom. How better could this have been expressed than in a bound copy of over 250 editorial gems with which he has graced the journal and edified our profession over 22 years? Though thus collected, they also remain dispersed in libraries throughout the world for the benefit of future generations of physicians.

LLOYD H. SMITH, Jr. MD

If he were a list-maker, Malcolm Stuart McNeal Watts would have volumes of lists. He could have a list of the titles of all of his editorials in *The Western Journal of Medicine*—more than 250 over the last 22 years. Mal never missed a beat; he never missed an issue. He could have a list of all of the physicians in California, and beyond, who know and respect him. That list itself would fill volumes because, in addition to his *WJM* editorship, he also brought public and private universities to the front lines of practice (and vice versa) via his long and hard work with Regional Medical Programs and Area Health Education Centers. Mal visited virtually every urban and rural practice site throughout California during his years of work in those two vineyards. Mal could also have a list, if he were boastful, which he is not, of all of the physicians for whom he has served as mentor. His integrity, insights, tenacity, broad world view; his ability to communicate and inspire action; his determination to do the right thing despite risk and sometimes pain have served as examples to his colleagues, young and old, for years. Some of the most effective people on local, regional, and national medical scenes today would not be as effective without Mal's example and sponsorship.

Mal Watts's own list of accomplishments includes, of course, the journal. He also lists the development of the concept of the California Medical Association's Scientific Advisory Panels, which represent the scientific and educational concerns of each specialty section and maintain professional standards through sponsorship of educational meetings at the association's annual meeting, furnish editorial consultation to the journal, and provide advice on scientific matters. Mal also recalls with pleasure that he brought medical students into the California Medical Association (CMA). His interest in young people stimulated successful integration of not only medical students but house officers into the structure and function of organized medicine.

As Holly Smith has mentioned, Mal has a remarkable and distinguished history: Trinity School, Harvard undergraduate and medical schools, Bellevue internship, University of California, San Francisco (UCSF), residency. After his army service during World War II—he's the first to admit that Seattle was not a hard-duty station—he went into practice with Dwight Wilbur, also one of the giants of American medicine of this century, who had taken over the editorship of *California Medicine* in 1946. Dwight nourished and expanded that journal and saw that there were even greater opportunities ahead. He feels that his greatest accomplishment was persuading Mal Watts and Lloyd H. Smith, Jr, then Chief of Medicine at UCSF, to become editor and associate editor, respectively, upon his retirement. Dwight has also left an imprint on the CMA itself, not only the journal. He chaired the ad hoc committee of the CMA Council that recommended the establishment of the Scientific Board to strengthen and formalize all scientific and educational activities conducted by the CMA.

Through the years, and even more so recently, Mal has had many awards and honors, including innumerable standing ovations. He is a member of the American Association for

the Advancement of Sciences, the Institute of Medicine of the National Academy of Sciences, and the California Academy of Medicine. He is a Clinical Professor at UCSF and was Associate Dean for 24 years. He is a Fellow of the American College of Physicians. He is on the Council of Biology Editors, is a member of the American Medical Writers Association, and shows his avocational interest by also being a member of the Society of Medical Friends of Wine. He has served volunteer stints on numerous boards, including the United Bay Area Crusade, Cathedral School, and the Rosenberg Foundation. He was elected to the CMA Council five years before he became editor of *The Western Journal of Medicine* and, as a member of the Council, of the Scientific Board, and the House of Delegates, has made a difference. He also writes for the *AMA News* and is incubating more editorials and a book. As editor of the journal, he is a member of the Vancouver Group, the international society of editors of distinguished medical journals. The United States has four representatives—the editors of the *Annals of Internal Medicine, JAMA, The New England Journal of Medicine,* and *WJM.*

A person is more than accomplishments. Mal is devoted to the symphony—and has good seats. He enjoys home and hearth and family. He is great of spirit. He is magnanimous, fair, constructive, optimistic yet realistic, and patient. And, fortunately for all of us, he is witty. Finally, he is charitable. The worst thing I have ever heard him say about anyone was that he was "one of a kind."

Malcolm Stuart McNeal Watts, too, is "one of a kind"—one of the best kind.

We all have a challenge ahead—and that is to hold the light of the journal high so it can continue to shine brightly, so it can continue to serve our patients and profession in science, in health, in public policy; so it can continue to inform and inspire. We are building on a firm foundation—43 years with two editors. Despite predictable and unpredictable problems, the journal will prevail.

LINDA HAWES CLEVER, MD

Volume 152 INDEX January-June 1990

## AUTHOR INDEX


Adamson, G. David, Stanford, California (Mar) 411
Adornato, Bruce T., Stanford, Calif (Apr) 427
Allport, Robert, San Francisco (Apr) 434
Amend, William J. C., Jr, San Francisco (Jun) 711
Anderson, Cynthia J., Salt Lake City (Mar) 298
Arai, Andrew, Portland (Apr) 383
Ashburn, William L., San Diego (Jun) 704
Ashton, Kenneth, Long Beach, Calif (Jun) 708

Bachman, Lea, San Francisco (May) 531
Bailie, Ira E., Turlock, Calif (Apr) 429
Balmes, John, San Francisco (Feb) 173
Balog, Janos, San Francisco (Jan) 76
Banisadre, Mussa, Modesto, Calif (Apr) 417
Bankowska, Jolanta, Sacramento, Calif (Jan) 78
Barnett, Paul G., Salinas, Calif (Mar) 317
Batki, Steven L., San Francisco (May) 547
Bauer, Douglas C., Palo Alto, Calif (Mar) 305
Baughan, David M., San Diego (Mar) 285
Becker, Bruce, Long Beach, Calif (Jun) 708
Becker, Charles E., San Francisco (Feb) 175, (May) 506
Benirschke, Kurt, San Diego (Jun) 716
Biakanja, Krist, San Francisco (Apr) 434
Birchfield, George R., Salt Lake City (Jun) 714
Blanc, Paul D., San Francisco (Feb) 181
Blaser, Martin J., Denver (Mar) 253
Blayney, Douglas W., Glendora, Calif (Apr) 426
Blossom, H. John, Fresno, Calif (Mar) 317
Blume, Karl G., Stanford, Calif (Jan) 46
Bodner, Anne J., Rockville, Md (Mar) 261
Bohnen, Robert F., Roseville, Calif (Apr) 417
Borgenicht, Louis, Salt Lake City (Feb) 185
Bouchard, Carla, San Bernardino, Calif (Jan) 87
Brandon, Jeffrey C., Orange, Calif (Jan) 65
Buller, Richard E., Irvine, Calif (Mar) 407
Burnett, William H., Sacramento, Calif (Mar) 317
Burrall, Barbara A., Davis, Calif (Mar) 268
Burrow, Gerard N., La Jolla, Calif (Apr) 427
Byrne, Thomas E., Chicago (Mar) 309
Byyny, Richard L., Denver (Apr) 392

Callaham, Michael L., San Francisco (Jun) 697
Cappelli, Susan, Cleveland (Feb) 190
Carretta, Robert F., Fair Oaks, Calif (Jun) 709
Casola, Giovanna, San Diego (Jan) 63
Chang, Yuan, Stanford, Calif (Apr) 427
Chao, Nelson J., Stanford, Calif (Jan) 46
Charles, Sara C., Chicago (Mar) 309
Chen, David C. P., Los Angeles (Jun) 708
Cheng, Tsung O., Washington, DC (Feb) 186
Chiu, John T., Newport Beach, Calif (Apr) 426
Christensen, Fred K., Scottsdale, Ariz (Apr) 439
Clark, H. Westley, San Francisco (May) 514
Clericuzio, Carol, Albuquerque (Apr) 418
Coffman, Byron, Cleveland (Feb) 190
Cooke, Molly, San Francisco (Jan) 57
Crain, Lucy S., San Francisco (Apr) 434
Crawshaw, Ralph, Portland (Apr) 441
Cunningham, George, Berkeley, Calif (Mar) 412
Curet, Luis, Albuquerque (Apr) 418
Cutler, Joel E., Portland (Jun) 677

D'Agostino, Horacio, San Diego (Jan) 64
Daniell, William, Seattle (Feb) 174
Danielson, Kelvin S., Scottsdale, Ariz (Apr) 439
Darmstadt, Gary L., La Jolla, Calif (Feb) 153
Davenport, Linda, San Francisco (May) 531
Davidson, Paul T., Los Angeles (Mar) 290
Davidson, Terence M., San Diego (Apr) 426
Davies, Michael L., Fort Meade, SD (Mar) 257
Davis, R. Jeffrey, Rancho Mirage, Calif (Jun) 719
Deutsch, Larry-Stuart, Orange, Calif (Jan) 65
Dickinson, Bill, Seattle (May) 604
Dietrich, Robert A., San Francisco (Feb) 192
DiSaia, Philip J., Irvine, Calif (Mar) 406
Diwan, Arwind, Honolulu (Mar) 261
Dixon, Peter S., Providence, RI (Mar) 261
DuPont, Robert L., Rockville, Md (May) 600
Dyer, Kirsti A., Davis, Calif (Feb) 195

Echeverria, Peter, Bangkok, Thailand (Mar) 253
Eichner, Robert, Portland (Feb) 194
Elson, David L., Sioux Falls, SD (Mar) 257
Erickson, Kenneth R., Portland (Feb) 159
Evans, Gary W., Bemidji, Minn (Jan) 41

Fajardo, Laurie L., Tucson (Mar) 301
Fan, Anna M., Sacramento, Calif (Jan) 78, (Mar) 286
Fein, George, San Francisco (May) 531
Felten, James A., Sacramento, Calif (Apr) 428
Fisher, Sarah, San Francisco (May) 531
Fitzgerald, Faith T., Sacramento, Calif (Apr) 377
Flaherty, Lawrence, Detroit (Jun) 714
Forman, Walter B., Albuquerque (Feb) 190
Franke, Kevin J., Chicago (Mar) 309
French, James W., Seattle (Mar) 308

Ganiats, Theodore G., San Diego (Mar) 285
Garty, Ben-Zion, Petah-Tiqva, Israel (Jan) 76
Geller, Jack, San Diego (Jan) 41
Gibson, R. Lawrence, Los Gatos, Calif (Apr) 427
Giudice, Linda C., Stanford, Calif (Mar) 408
Glode, Mary P., Denver (Mar) 253
Goetz, Matthew B., Sepulveda, Calif (Mar) 296
Gold, Ellen B., Davis, Calif (Feb) 172
Gold, Mark S., Summit, NJ (May) 573
Goldman, Lynn R., Emeryville, Calif (Mar) 289
Gonzalez, Richard I., Stanford, Calif (Apr) 430
Gonzalez, Steven M., Caldwell, Idaho (Apr) 430
Gordon, Jeoffry B., San Diego (Jun) 723
Gottlieb, Fred, Sacramento, Calif (Jan) 82
Gottlieb, Michael S., Sherman Oaks, Calif (Mar) 288
Grant, Edward G., Los Angeles (Jan) 62
Grimes, David A., Los Angeles (Mar) 410
Gulbrandson, Rolf N., Roseville, Calif (Apr) 417
Guyatt, Gordon H., Hamilton, Ontario (Jan) 67

Haan, Mary, Emeryville, Calif (Mar) 289
Hall, Bruce M., Stanford, Calif (Jun) 687
Haller, John S., Jr, Denver (Jun) 729
Halperin, Blair D., Denver (Jun) 677
Halpern, Georges M., Davis, Calif (Mar) 268
Hanafee, William N., Los Angeles (Jan) 66
Hanh, Le Quoc, Los Angeles (Mar) 290
Harber, Philip, Los Angeles (Feb) 175
Harris, Cheryl P., Salt Lake City (Jan) 77
Hasso, Anton N., Loma Linda, Calif (Jan) 63
Haygood, Tamara Miner, Albuquerque (Jan) 64
Hendricks, Rickey, San Francisco (Apr) 450
Hensleigh, Paul A., Santa Clara, Calif (Mar) 407
Herrick, Maie, Stanford, Calif (Apr) 427
Hertsgaard, David B., Orange, Calif (Apr) 450
Hertz, Dwight, Sioux Falls, SD (Mar) 257
Heseltine, P. N. R., Los Angeles (Apr) 423
Heyworth, Martin F., San Francisco (Mar) 293
Hiatt, Patricia, San Francisco (Feb) 181
Hickok, Lee R., Portland (Mar) 411
Hink, Robert H., Berkeley, Calif (May) 585
Hoegerman, Georgeanne, Richmond, Va (May) 559
Hoffman, Richard E., Denver (Jan) 75
Hofmann, Alan F., San Diego (Jan) 64
Holbrook, John H., Salt Lake City (Feb) 184
Holbrook, R. Harold, Stanford, Calif (Mar) 407
Horoupian, Dikran, Stanford, Calif (Apr) 427
Huntley, Arthur C., Davis, Calif (Mar) 268

Ikeda, Richard, Sacramento, Calif (May) 617
Imam, A. Ali, Irvine, Calif (Mar) 313
Izquierdo, Luis, Albuquerque (Apr) 418

Jabour, Bradley A., Los Angeles (Jan) 66
Jackson, Richard J., Sacramento, Calif (Jan) 78, (Mar) 286
Janoff, Edward N., Denver (Mar) 253
Jarvis, William T., Loma Linda, Calif (Jan) 87
Jessup, Marty, Berkeley, Calif (May) 553
Jodar, Vaughn A., Sacramento, Calif (Apr) 428
Johnston, Joyce, Loma Linda, Calif (Jan) 67

Karan, Lori D., Richmond, Va (May) 538
Kardos, Gary G., San Francisco (Jan) 95
Katz, Steven J., Seattle (Jun) 683
Kauli, Rivka, Petah-Tiqva, Israel (Jan) 76
Kennedy, Charles A., Sepulveda, Calif (Mar) 296
Kettel, L. Michael, San Diego (Mar) 408
Kirk, Gerald, Loma Linda, Calif (Jun) 706
Kizer, Kenneth W., Sacramento, Calif (Jan) 78, (Mar) 289, (Apr) 428
Klein, Gerald L., San Diego (Mar) 313
Klonecke, Andrew S., Stanford, Calif (Jun) 704
Krajeski, James P., San Francisco (Jun) 723
Kramer, Barry Alan, Los Angeles (Jan) 77
Kresch, Arnold, Stanford, Calif (Mar) 409
Kron, Jack, Portland (Apr) 383, (Jun) 677
Kudenchuk, Peter J., Seattle (Jun) 677
Kushnir, Ori, Albuquerque (Apr) 418

Lambert, Elaine, Stanford, Calif (Apr) 427
Lammer, Edward, Emeryville, Calif (Jan) 67
Larson, Eric B., Seattle (Jan) 52
Lawry, George V., Stanford, Calif (Apr) 427
Lee, Philip R., San Francisco (Mar) 277
Levin, Ralph, San Mateo, Calif (Jan) 77
Levy, Jonathan M., Scottsdale, Ariz (Jan) 93, (Apr) 439
Lewis, David H., Seattle (Jun) 705
Ling, Walter, Los Angeles (May) 565
Litovitz, Toby L., Washington, DC (Feb) 178
London, Stephanie J., Los Angeles (Feb) 172
Lufkin, Robert A., Los Angeles (Jan) 66
Lundberg, Max S., Salt Lake City (Mar) 298
Lyman, Donald O., Sacramento, Calif (Jan) 78
Lyons, Kenneth P., Long Beach, Calif (Jun) 708

McAnulty, John H., Portland (Jun) 677
McCutchan, J. Allen, San Diego (Jun) 716
McDougall, I. Ross, Stanford, Calif (Jun) 704
McGahan, John P., Sacramento, Calif (Jan) 63
MacLean, Charles, Honolulu (Jan) 37
McMillin, Michael, Sioux Falls, SD (Mar) 257
Maizlish, Neil, Berkeley, Calif (Feb) 181
Malone, Joseph L., San Diego (Feb) 188
Mangravite, Donald N., San Francisco (Apr) 434
Markell, Edward K., Oakland, Calif (Jun) 721
Mathisen, Glenn, Sylmar, Calif (Mar) 296
Melcher, William L., San Francisco (Feb) 192
Meltzer, Eli O., San Diego (Mar) 313
Micik, Sylvia, San Diego (Mar) 287, 288
Midtling, John E., Milwaukee (Mar) 317
Milbourne, Andrea, Honolulu (Mar) 261
Milki, Amin, Stanford, Calif (Mar) 410
Monahan, Brian, Bethesda, Md (Feb) 188
Montes, Jean M., Sacramento, Calif (Apr) 428
Moossazadeh, Jamshid, Stanford, Calif (Mar) 410
Morrison, Martha A., Atlanta (May) 543
Morton, Alice, San Bernardino, Calif (Jan) 87

Nakamura, Jeffrey M., Honolulu (Mar) 261
Nelp, Wil B., Seattle (Jun) 705
Nelson, Robert M., San Francisco (Apr) 447
Nestor, James J., Santa Clara, Calif (Feb) 185
Nishiwaki, Robin, San Bernardino, Calif (Jan) 87
Novey, Harold S., Irvine, Calif (Mar) 313
Nussbaum, Joseph M., Los Angeles (Apr) 423

Okihiro, Michael, Honolulu (Mar) 261
Oldfield, Edward C., San Diego (Feb) 188
Olney, Patricia, Albuquerque (Apr) 418
Olney, Richard, Gallup, NM (Apr) 418
Olson, Kent R., San Francisco (Feb) 181
Oppenheim, Elliott B., Bellevue, Wash (Feb) 196
Orgel, H. Alice, San Diego (Mar) 313
Osborn, Lucy M., Salt Lake City (Mar) 322
Osterloh, John D., San Francisco (May) 506
Oye, Robert K., Los Angeles (Jun) 683

Paparello, Scott, Bethesda, Md (Feb) 188
Parker, Frank, Portland (Feb) 187
Payte, J. Thomas, San Antonio, Tex (May) 588
Pelton, Chet, Sacramento, Calif (May) 617
Pennington, Daniel W., San Francisco (Apr) 421
Pennington, James E., Berkeley, Calif (Apr) 401
Peters, James A., Loma Linda, Calif (Jan) 87
Peters, John M., Los Angeles (Feb) 172
Peterson, Walter L., Dallas (Feb) 167
Pond, Gerald D., Tucson (Mar) 308
Press, Raymond I., San Diego (Jan) 41

Pun, Chiu O., Shatin, Hong Kong (Feb) 149
Pyskoty, Charlene E., Chicago (Mar) 309

Radcliffe, Anthony B., Fontana, Calif (May) 604
Raevsky, Cathy, Denver (Jan) 75
Ramanathan, Subramanyam, Honlulu (Jan) 37
Redlich, Carrie A., Seattle (Feb) 176
Redman, Bruce G., Detroit (Jun) 714
Reiser, Jody, Tucson (Apr) 439
Rempel, David, Berkeley, Calif (Feb) 181
Renneker, Mark, San Francisco (Jan) 90
Rickman, Leland S., Bethesda, Md (Feb) 188
Robbins, John, Sacramento, Calif (Jan) 82
Ronaghy, H. A., La Jolla, Calif (Jun) 723
Rosenberg, Robert, Albuquerque (Jan) 64
Rubin, Haya R., San Francisco (Jun) 722
Rude, Robert K., Los Angeles (Feb) 145
Rush, Peter A., Fontana, Calif (May) 604
Rutberg, L. David, La Mesa, Ariz (Feb) 185
Ryzen, Elisabeth, Los Angeles (Feb) 145

Safrin, Richard E., San Diego (Jun) 722
Sakala, Elmar P., Loma Linda, Calif (Jan) 67
Samaan, Naguib A., Houston (Jan) 72
Samet, Jonathan M., Albuquerque (Feb) 174
Samlowski, Wolfram E., Salt Lake City (Jun) 714
Sanchez, Diane, Albuquerque (Apr) 418
Sarti, Dennis A., Los Angeles (Jan) 65
Sarto, Gloria E., Albuquerque (Apr) 418
Schatz, Irwin J., Honolulu (Jan) 37
Schenker, Marc B., Davis, Calif (Feb) 173
Scherger, Joseph E., Davis, Calif (Jan) 92
Schlag, Robert D., Emeryville, Calif (Mar) 289
Schnoll, Sidney H., Richmond, Va (May) 559
Schour, Marianne, San Francisco (Apr) 434
Schwartz, Ivy, Tucson (Mar) 290, (Jun) 725
Sees, Karen Lea, San Francisco (May) 578
Sheehan, Denice, Cleveland (Feb) 190
Shimamura, Arthur P., Berkeley, Calif (Feb) 177
Shore, William B., San Francisco (Apr) 449
Shusterman, Dennis, Berkeley, Calif (Jun) 721
Siegel, Michael E., Los Angeles (Jun) 708, 709
Signer, Stephen F., San Diego (Jun) 719
Silk, Arthur D., Garden Grove, Calif (Jan) 75, (Feb) 186
Smith, David E., San Francisco (May) 500, 613
Smith, William McFate, Berkeley, Calif (Apr) 414
Spruance, Spots' ood L., Salt Lake City (Mar) 298
Stein, Martin, Stanford, Calif (Apr) 427
Steinman, Howard K., La Jolla, Calif (Feb) 153
Stephens, Mark G., Tucson (Jan) 93
Stulbarg, Michael S., San Francisco (Apr) 421
Suranyi, Michael G., Stanford, Calif (Jun) 687
Swensen, Ron E., Stanford, Calif (Mar) 406

Tashkin, Donald P., Los Angeles (May) 525
Taylor, David N., Bangkok, Thailand (Mar) 253
Taylor, Wanda A., Summit, NJ (May) 573
Tessler, Franklin N., Los Angeles (Jan) 62
Thurmond, Ellen, Richmond, Va (May) 559
Townsend, Jeannette J., Salt Lake City (Jan) 77

Udkow, Michael P., Oakland, Calif (Jun) 721
Umland, Berthold E., Albuquerque (Jun) 721
Updike, Wanda S., Salt Lake City (Mar) 298

Van Ness, Paul C., Cleveland (Jun) 719
vanSonnenberg, Eric, San Diego (Jan) 64
Venkatesh, Swamy, Houston (Jan) 72
Vernon, Thomas M., Denver (Jan) 75
Villagomez, Rosie, Honolulu (Jan) 37
Vogel, John Max, Sacramento, Calif (Jun) 707

Wagner, Kenneth F., Bethesda, Md (Feb) 188
Wallace, John, Newport, RI (May) 502
Ward, John H., Salt Lake City (Jun) 714
Warnock, Martha L., San Francisco (Apr) 421
Washington, A. Eugene, San Francisco (Mar) 413
Wasserman, Stephen I., San Diego (Mar) 292
Watts, Malcolm S. M., San Francisco (Jan) 68, (Feb) 180, (Mar) 292, (Apr) 414, (May) 499, (Jun) 711
Weiler, Philip G., Davis, Calif (Mar) 286
Wesson, Donald R., San Francisco (May) 565, 585, 613
Whitcomb, Barbara, Denver (Apr) 392
White, J. Douglas, Washington, DC (Feb) 178
Whitlock, Warren L., San Francisco (Feb) 192
Wilford, Bonnie B., Chicago (May) 609

Williams, Walter H., Tucson (Jun) 707
Williamson, Michael R., Albuquerque (Jan) 64
Wilson, Catherine A., Richmond, Va (May) 559
Wolf, Frederick C., Denver (Jan) 75
Woo, Kam S., Shatin, Hong Kong (Feb) 149
Wood, Rachel C., Denver (Jan) 75
Wu, Albert W., San Francisco (Jun) 716, 722

Yamamoto, Hiroshi E., Sacramento, Calif (Apr) 428
Yuwiler, Janice, San Diego (Mar) 287, 288

Zanjani, Esmail D., Reno, Nev (Apr) 417
Ziering, Robert W., San Diego (Mar) 313
Zonis, Richard D., Scottsdale, Ariz (Apr) 439
Zweben, Joan Ellen, Oakland, Calif (May) 588

## IN MEMORIAM

*Arizona Medical Association:*

Atkinson, George S., Dec 12, 1989 (Mar) 250
Collings, Robert Z., Feb 25, 1990 (May) 479
Craig, Carlos C., Jan 20, 1990 (Mar) 250
Crosbie, Stanley B., Dec 22, 1989 (Mar) 250
Ford, Lattimer H., Feb 1, 1990 (May) 479
Giese, Theodore M., Mar 9, 1990 (May) 479
Griffin, C. Clayton, Nov 19, 1989 (Mar) 250
Hicks, T. J., Sep 8, 1989 (Jan) 6
MacGregor, Robert J., Jun 30, 1989 (Jan) 6
Oyler, Raymond F., Nov 17, 1989 (Mar) 250
Vivian, Charles W., Apr 29, 1989 (Mar) 250
Voldeng, Karl E., Nov 13, 1989 (Mar) 250

*California Medical Association:*

Amdur, Richard D., Jan 4, 1990 (May) 479
Bethel, Robert D., Oct 5, 1989 (May) 479
Boggs, Robert W., Feb 1990 (May) 479
Brown, Howard A., Feb 1990 (May) 479
Buck, Lilia, Feb 1, 1990 (May) 479
Burre, Samuel Pink, Oct 24, 1989 (Jan) 6
Campbell, Alice, Jul 20, 1989 (May) 479
Cheung, Joseph, Jan 26, 1990 (May) 479
Clark, Darrel Grant, Feb 25, 1990 (May) 479
Clary, Raimond F., Feb 20, 1990 (May) 479
Crozier, Henry C., Jan 24, 1990 (May) 479
DeVaul, Charles H., Feb 12, 1990 (May) 479
Duncan, Ray Hamilton, Dec 23, 1989 (May) 479
Eaton, Charles H., Jan 18, 1990 (May) 479
Fessler, Francis W., Oct 27, 1989 (Jan) 6
Flood, Randolph G., Oct 9, 1989 (May) 479
Gallup, Charles A., Aug 27, 1989 (May) 479
Globerson, Irwin, Feb 26, 1990 (May) 479
Grant, Sidney, Feb 11, 1990 (May) 479
Greer, Edwin D., Dec 7, 1989 (May) 479
Haasch-Chess, Dorothy Anne, Jan 2, 1990 (May) 479
Halley, Edmund P., Sep 29, 1989 (Jan) 6
Harper, Howard E., Jan 22, 1990 (May) 479
Harrington, David O., Feb 18, 1990 (May) 479
Hartman, John R., Jan 26, 1990 (May) 479
Harwood, David, Dec 24, 1989 (May) 479
Hemminger, George W., Sep 15, 1989 (May) 479
Higa, Melvin Tsugio, Dec 5, 1989 (May) 479
Howard, John R., Feb 5, 1990 (May) 479
Hsu, Chi-Pen, Feb 3, 1990 (May) 479
Hunt, Irene M., Feb 1, 1990 (May) 479
Husted, Russell M., Jul 14, 1989 (May) 479
Jaekle, Russell, Dec 17, 1989 (May) 479
Jergesen, Floyd H., Feb 20, 1990 (May) 479
Jones-Soto, Nancy M., Nov 1989 (May) 479
Klaumann, Benjamin F., Nov 29, 1989 (May) 485
Lambert, Richard H., Sep 27, 1989 (Jan) 6
Maher, John A., Feb 5, 1990 (May) 485
Mallary, Charles R., Mar 11, 1990 (May) 485
Marcus, Simson, Nov 15, 1989 (May) 485
Melinkoff, Eugene, Dec 23, 1989 (May) 485
Myatt, John P., Nov 9, 1989 (May) 485
Naess, Erling W., Dec 12, 1989 (May) 485
Norins, Howard, Feb 16, 1990 (May) 485
Odebrecht, Paul L., Feb 1990 (May) 485
Orwig, James B. III, Sep 16, 1989 (Jan) 6
Peterfy, Richard A., Jan 28, 1990 (May) 485
Reade, Frank Z., Jan 22, 1990 (May) 485
Rey, George E., Aug 12, 1989 (Jan) 6
Reynolds, Terry N., Jan 29, 1990 (May) 485
Robinson, Clinton W., Jun 4, 1989 (May) 485
Robson, Philip G., Aug 20, 1989 (May) 485
Saltzer, Arthur, Sep 26, 1989 (May) 485
Schilling, Melvin, Oct 14, 1989 (May) 485
Shon, Charles M., Oct 4, 1989 (Jan) 6
Smallberg, William, Feb 9, 1990 (May) 485
Somers, Raymond H., Sep 30, 1989 (Jan) 6
Stallone, Victor, Jr, Jan 22, 1990 (May) 485
Stanton, James T., Nov 1, 1989 (Jan) 6
Stein, Jack L., Dec 18, 1989 (May) 485
Sturm, Avery E., Jul 3, 1989 (May) 485
Thorpe, James Hancock, Dec 23, 1989 (May) 485
Truman, James C., Dec 1989 (May) 485
Tucker, William W., Dec 10, 1989 (May) 485
Walker, J. Fred, Aug 1989 (Jan) 6

*Denver Medical Society:*

Lipan, Edward M., Oct 16, 1989 (Jan) 6
Verploeg, Ralph H., Oct 31, 1989 (Jan) 6

*New Mexico Medical Society:*

Follingstad, Alvin H., Oct 19, 1989 (Jan) 6

*Utah Medical Association:*

Benedict, Roland Dean, Dec 16, 1989 (Mar) 250

## SUBJECT INDEX

### A

Abuse of Prescription Drugs (Addiction Medicine), Bonnie B. Wilford (May) 609
Academic Medicine (Correspondence), L. David Rutberg (Feb) 185
Acoustic Neuromas (Correspondence), James J. Nestor (Feb) 185
Acquired Immunodeficiency Syndrome, see *Rhabdomyolysis and Staphylococcus aureus Septicemia in a Man With*
Acute Abdomen, see *Tropical Pyomyositis of the Abdominal Wall Musculature Mimicking*
Acute Pancreatitis Associated With High-Dose Interleukin-2 Immunotherapy for Malignant Melanoma, George R. Birchfield, John H. Ward, Bruce G. Redman, Lawrence Flaherty, Wolfram E. Samlowski (Jun) 714

**Addiction Medicine:**

Addiction Medicine, Malcolm S. M. Watts (May) 499
Addiction Medicine and the Primary Care Physician, David E. Smith (May) 500
New Disease Model of Alcoholism, John Wallace (May) 502
Chemical Dependency and Drug Testing in the Workplace, John D. Osterloh, Charles E. Becker (May) 506
Role of Physicians as Medical Review Officers in Workplace Drug Testing Programs—In Pursuit of the Last Nanogram, H. Westley Clark (May) 514
Pulmonary Complications of Smoked Substance Abuse, Donald P. Tashkin (May) 525
Cognitive Impairments in Abstinent Alcoholics, George Fein, Lea Bachman, Sarah Fisher, Linda Davenport (May) 531
Primary Care for AIDS and Chemical Dependence, Lori D. Karan (May) 538
Addiction in Adolescents, Martha A. Morrison (May) 543
Drug Abuse, Psychiatric Disorders, and AIDS—Dual and Triple Diagnosis, Steven L. Batki (May) 547
Treatment of Perinatal Addiction—Identification, Intervention, and Advocacy, Marty Jessup (May) 553
Drug-Exposed Neonates, Georgeanne Hoegerman, Catherine A. Wilson, Ellen Thurmond, Sidney H. Schnoll (May) 559
Drugs of Abuse—Opiates, Walter Ling, Donald R. Wesson (May) 565
Pharmacologic Approaches to the Treatment of Cocaine Dependence, Wanda A. Taylor, Mark S. Gold (May) 573
Cigarette Smoking, Nicotine Dependence, and Treatment, Karen Lea Sees (May) 578
Expert Systems in Treating Substance Abuse, Donald R. Wesson, Robert H. Hink (May) 585
Methadone Maintenance in the Treatment of Opioid Dependence—A Current Perspective, Joan Ellen Zweben, J. Thomas Payte (May) 588
Physician's Guide to Discontinuing Benzodiazepine Therapy, Robert L. DuPont (May) 600
Alprazolam Use and Dependence—A Retrospective Analysis of 30 Cases of Withdrawal, Bill Dickinson, Peter A. Rush, Anthony B. Radcliffe (May) 604
Abuse of Prescription Drugs, Bonnie B. Wilford (May) 609

Prescription Drug Abuse—Patient, Physician, and Cultural Responsibilities, Donald R. Wesson, David E. Smith .... (May) 613
Diversion Programs for Impaired Physicians, Richard Ikeda, Chet Pelton ..... (May) 617

Adenocarcinoma, see *Erythrocytosis Caused by an Erythropoietin-Producing Breast*
After Shock (Lessons From the Practice), Mark Renneker ... (Jan) 90
AIDS, see *Drug Abuse, Psychiatric Disorders, and*
AIDS, see *Primary Care for*
Alcoholic Cirrhosis and Cardiomyopathy (Correspondence), Tsung O. Cheng ..... (Feb) 186
Alcoholics, see *Cognitive Impairments in Abstinent*
Alcoholism, see *New Disease Model of*
Allergy, see *Simplified Screening Test for the Diagnosis of*
Allotransplantation Facilitated by In Utero Diagnosis of Hypoplastic Left-Sided Heart Syndrome, see *Neonatal Cardiac*
Alopecia Universalis in Autoimmune Polyglandular Syndrome Type I (Correspondence), Ben-Zion Garty, Kivka Kauli ..... (Jan) 76
Alprazolam Use and Dependence—A Retrospective Analysis of 30 Cases of Withdrawal (Addiction Medicine), Bill Dickinson, Peter A. Rush, Anthony B. Radcliffe ..... (May) 604
Amnestic Disorders—Pathophysiology and Patterns of Memory Dysfunction (Medical Progress), Kenneth R. Erickson .... (Feb) 159
Editorial, Arthur P. Shimamura ..... (Feb) 177
Anemia, see *Zinc Abuse—An Unsuspected Cause of Sideroblastic*
Apolipoprotein Fractions in Human Subjects, see *Effect of Chromium Picolinate on Serum Cholesterol and*
Association of Spontaneous Pneumomediastinum With Substance Abuse, Laurie L. Fajardo ..... (Mar) 301
Asthma Deaths (Correspondence), John T. Chiu ..... (Apr) 426
Autoimmune Polyglandular Syndrome Type I, see *Alopecia Universalis in*

B

Benzodiazepine Therapy, see *Physician's Guide to Discontinuing*
Bernstein's Hug (Lessons From the Practice), Elliott B. Oppenheim ..... (Feb) 196
Biological Significance of *Giardia*-Specific Antibodies, Martin F. Heyworth ..... (Mar) 293
*Blastocystis hominis* (Correspondence), Edward K. Markell, Michael P. Udkow ..... (Jun) 721
Bone Marrow Transplantation. Part II—Antologous (Medical Progress), Nelson J. Chao, Karl G. Blume ..... (Jan) 46

**Book Reviews:**

Common Skin Disorders—A Physician's Illustrated Manual With Patient Instruction Sheets—2nd Edition, *Epstein* ..... (Feb) 187
Diagnostic Nuclear Medicine, *Gottschalk et al* ..... (Apr) 450
Grand Rounds—One Hundred Years of Internal Medicine, *Maulitz & Long* ..... (Apr) 450
Heart Disease in Infants, Children, and Adolescents, *Adams, Emmanouilides, Riemenschneider* ..... (Mar) 308
Intensive Care—Facing the Critical Choices, *Raffin et al* .... (Feb) 184
Interventional Radiology, *Castañeda-Zuñiga & Tadavarthy* .. (Mar) 316
Preventing Emergency Medicine Malpractice, *Fish & Ehrhardt* ..... (Feb) 194

Brain Abscess, see *Successful Medical Treatment of Listerial*
Breast Adenocarcinoma, see *Erythrocytosis Caused by an Erythropoietin-Producing*

C

California, see *Future of Family Practice Training in*
[Canadian Health Care System], see *Eye of the Beholder*
Capgras's Syndrome Associated With Sensory Loss, Stephen F. Signer, Paul C. Van Ness, R. Jeffrey Davis .... (Jun) 719
Carcinoid and Multiple Endocrine Neoplasia, see *Thymic*
Carcinoid Tumors of the Thymus, Swamy Venkatesh, Naguib A. Samaan ..... (Jan) 72
Correspondence, Douglas W. Blayney ..... (Apr) 426
Cardiac Allotransplantation Facilitated by In Utero Diagnosis of Hypoplastic Left-Sided Heart Syndrome, see *Neonatal*
Cardiac Arrest, see *High-Dose Epinephrine Therapy and Other Advances in Treating*
Cardiomyopathy, see *Alcoholic Cirrhosis and*
Catecholamines, and α-Adrenergic Receptors in Mitral Valve Prolapse, see *Orthostatic Hypotension,*
Chemical Dependence, see *Primary Care for AIDS and*
Chemical Dependency and Drug Testing in the Workplace (Addiction Medicine), John D. Osterloh, Charles E. Becker ..... (May) 506
Children in Developmental Centers, see *Health Care Needs and Services for Technology-Dependent*
Chromium Picolinate on Serum Cholesterol and Apolipoprotein Fractions in Human Subjects, see *Effect of*
Chronic Disease, see *Two Generations—Reflections on Changes in the Treatment of a*
Chronic Urticaria (Medical Progress), Barbara A. Burrall, Georges M. Halpern, Arthur C. Huntley ..... (Mar) 268
Chylothorax and Respiratory Failure in Kaposi's Sarcoma, Daniel W. Pennington, Martha L. Warnock, Michael S. Stulbarg ..... (Apr) 421
Cigarette Smoking, Nicotine Dependence, and Treatment (Addiction Medicine), Karen Lea Sees ..... (May) 578

**Clinical Investigation:**

Effect of Chromium Picolinate on Serum Cholesterol and Apolipoprotein Fractions in Human Subjects, Raymond I. Press, Jack Geller, Gary W. Evans ..... (Jan) 41
Low Intracellular Magnesium in Patients With Acute Pancreatitis and Hypocalcemia, Elisabeth Ryzen, Robert K. Rude ..... (Feb) 145
Misdiagnosing Ventricular Tachycardia in Patients With Underlying Conduction Disease and Similar Sinus and Tachycardia Morphologies, Blair D. Halperin, Jack Kron, Joel E. Cutler, Peter J. Kudenchuk, John H. McAnulty ..... (Jun) 677
Orthostatic Hypotension, Catecholamines, and α-Adrenergic Receptors in Mitral Valve Prolapse, Irwin J. Schatz, Subramanyam Ramanathan, Rosie Villagomez, Charles MacLean ..... (Jan) 37
Serum Antibodies to *Giardia lamblia* by Age in Populations in Colorado and Thailand, Edward N. Janoff, David N. Taylor, Peter Echeverria, Mary P. Glode, Martin J. Blaser ..... (Mar) 253
Editorial, Martin F. Heyworth ..... (Mar) 293

**Clinical Review:**

Mohs' Micrographic Surgery of the Head and Neck, Gary L. Darmstadt, Howard K. Steinman ..... (Feb) 153
Correspondence, Richard E. Safrin ..... (Jun) 722

Cocaine Dependence, see *Pharmacologic Approaches to the Treatment of*
Cognitive Impairments in Abstinent Alcoholics (Addiction Medicine), George Fein, Lea Bachman, Sarah Fisher, Linda Davenport ..... (May) 531
Cognitive Testing in Internal Medicine House Staff, see *Sleep Deprivation and*
Confidential Versus Anonymous Human Immunodeficiency Virus Antibody Testing (Correspondence), Richard E. Hoffman, Frederick C. Wolf, Rachel C. Wood, Cathy Raevsky, Thomas M. Vernon ..... (Jan) 75
James P. Krajeski ..... (Jun) 723

**Correspondence:**

Academic Medicine, L. David Rutberg ..... (Feb) 185
Acoustic Neuromas, James J. Nestor ..... (Feb) 185
Alcoholic Cirrhosis and Cardiomyopathy, Tsung O. Cheng ... (Feb) 186
Alopecia Universalis in Autoimmune Polyglandular Syndrome Type 1, Ben-Zion Garty, Kivka Kauli ..... (Jan) 76
Asthma Deaths, John T. Chiu ..... (Apr) 426
*Blastocystis hominis*, Edward K. Markell, Michael P. Udkow (Jun) 721
Confidential Versus Anonymous Human Immunodeficiency Virus Antibody Testing, Richard E. Hoffman, Frederick C. Wolf, Rachel C. Wood, Cathy Raevsky, Thomas M. Vernon ..... (Jan) 75
James P. Krajeski ..... (Jun) 723
Cost of Medicine, Arthur D. Silk ..... (Jan) 75
Dialysis Disequilibrium Syndrome, Ralph Levin ..... (Jan) 77
Reply, Cheryl P. Harris, Jeannette J. Townsend ..... (Jan) 77
Electroconvulsive Therapy Use During Pregnancy, Barry Alan Kramer ..... (Jan) 77
Espresso Maker's Wrist, Dennis Shusterman ..... (Jun) 721
Eye of the Beholder, Gerard N. Burrow ..... (Apr) 427
Iatrogenic Illness, Terence M. Davidson ..... (Apr) 426
Integration of Prevention Efforts, Kenneth W. Kizer, James A. Felten, Vaughn A. Jodar, Hiroshi E. Yamamoto, Jean M. Montes ..... (Apr) 428
Is It Fair to Blame the Victim?, Arthur D. Silk ..... (Feb) 186
Life-Style and Illness, Ira E. Bailie ..... (Apr) 429
National Health Insurance in America—The Issue of Copayment, Janos Balog ..... (Jan) 76
Pathologist's View of Mohs' Micrographic Surgery, Richard E. Safrin ..... (Jun) 722
Patients' Presence in Prenatal Screening, Berthold E. Umland (Jun) 721
Putting Practice Into Law, Jeoffry B. Gordon ..... (Jun) 723

Ruminations of an Aspiring Californian, Albert W. Wu, Haya R. Rubin ... (Jun) 722
Thymic Carcinoid and Multiple Endocrine Neoplasia, Douglas W. Blayney ... (Apr) 426
Trust, Louis Borgenicht ... (Feb) 185
Tryptophan Use and Fasciitis, Bruce T. Adornato, Yuan Chang, Dikran Horoupian, Maie Herrick, Elaine Lambert, George V. Lawry, Martin Stein ... (Apr) 427
War on Drugs, R. Lawrence Gibson ... (Apr) 427
Zinc, H. A. Ronaghy ... (Jun) 723

Cost of Medicine (Correspondence), Arthur D. Silk ... (Jan) 75
Current Management of the Wolff-Parkinson-White Syndrome, Andrew Arai, Jack Kron ... (Apr) 383
Current Status of Renal Transplantation (Medical Progress), Michael G. Suranyi, Bruce M. Hall ... (Jun) 687
Editorial, William J. C. Amend, Jr ... (Jun) 711
Cystic Hygroma and Hydrops, see *Prenatal Diagnosis of Noonan's Syndrome in a Female Infant With Spontaneous Resolution of*

## D

Developing Principles for Prudent Health Care Allocation—The Continuing Oregon Experiment (In the Forefront), Ralph Crawshaw ... (Apr) 441
Developmental Centers, see *Health Care Needs and Services for Technology-Dependent Children in*
Diabetes Mellitus, see *Syndrome of Plasma Cell Dyscrasia, Polyneuropathy, and*
Dialysis Disequilibrium Syndrome (Correspondence), Ralph Levin ... (Jan) 77
Reply, Cheryl P. Harris, Jeannette J. Townsend ... (Jan) 77
Diversion Programs for Impaired Physicians (Addiction Medicine), Richard Ikeda, Chet Pelton ... (May) 617
Drug Abuse, Psychiatric Disorders, and AIDS—Dual and Triple Diagnosis (Addiction Medicine), Steven L. Batki ... (May) 547
Drug-Exposed Neonates (Addiction Medicine), Georgeanne Hoegerman, Catherine A. Wilson, Ellen Thurmond, Sidney H. Schnoll ... (May) 559
Drugs, see *War on*
Drugs of Abuse—Opiates (Addiction Medicine), Walter Ling, Donald R. Wesson ... (May) 565
Drug Testing in the Workplace, see *Chemical Dependency and*
Drug Testing Programs—In Pursuit of the Last Nanogram, see *Role of Physicians as Medical Review Officers in Workplace*
Dupuytren's Disease (Topics in Primary Care Medicine), Steven M. Gonzalez, Richard I. Gonzalez ... (Apr) 430

## E

[Earthquake], see *After Shock*

### Editorials:

Are Vitamin A Supplements Needed During Pregnancy?, Edward Lammer ... (Jan) 67
Biological Significance of *Giardia*-Specific Antibodies, Martin F. Heyworth ... (Mar) 293
Chronic Urticaria—A Frustrating but Increasingly Understandable Disorder, Stephen I. Wasserman ... (Mar) 292
Health Care—Where Are the Problems and Where Are the Solutions? ... (Jan) 68
Correspondence, Ira E. Bailie ... (Apr) 429
Hypertension in the Elderly, William McFate Smith ... (Apr) 414
Kidney Transplant Revisited (1990), William J. C. Amend, Jr (Jun) 711
Medicine in Extraordinary Times ... (Jun) 711
Memory and Amnesia, Arthur P. Shimamura ... (Feb) 177
N-of-1 Randomized Trials—Where Do We Stand?, Gordon H. Guyatt ... (Jan) 67
Occupational and Environmental Illness and the Poison Center, Toby L. Litovitz, J. Douglas White ... (Feb) 178
On Rocks and Hard Places ... (Feb) 180
Physicians as Role Models in Society ... (Mar) 292
Three Possible Futures for Medicine ... (Apr) 414

Editorials, see *Special*
Effect of Chromium Picolinate on Serum Cholesterol and Apolipoprotein Fractions In Human Subjects (Clinical Investigation), Raymond I. Press, Jack Geller, Gary W. Evans ... (Jan) 41
Elderly, see *Perspective on Hypertension in the*
Electroconvulsive Therapy Use During Pregnancy (Correspondence), Barry Alan Kramer ... (Jan) 77
Endocrine Neoplasia, see *Thymic Carcinoid and Multiple*
Epinephrine Therapy and Other Advances in Treating Cardiac Arrest, see *High-Dose*

### Epitomes:

#### Nuclear Medicine:

Single-Photon-Emission Computed Tomographic Imaging of the Bone, Andrew S. Klonecke, I. Ross McDougall ... (Jun) 704
Single-Photon-Emission Computed Tomography Using Cerebral Perfusion, William L. Ashburn ... (Jun) 704
Single-Photon-Emission Computed Tomography of Myocardial Perfusion and the Hepatic Blood Pool, David H. Lewis, Wil B.Nelp ... (Jun) 705
Gastric Emptying Revisited, Gerald Kirk ... (Jun) 706
Hepatobiliary Excretion Scintigraphy Revisited, Walter H. Williams ... (Jun) 707
Captopril Renograms for Detecting Renovascular Hypertension, John Max Vogel ... (Jun) 707
Dacryoscintigraphy Revisited, Kenneth P. Lyons, Bruce Becker, Kenneth Ashton ... (Jun) 708
Radiolabeled Monoclonal Antibodies for Detecting and Treating Cancer, David C. P. Chen, Michael E. Siegel ... (Jun) 708
Treatment of Bone Metastases, Robert F. Carretta ... (Jun) 709
Radionuclide Synovectomy for Chronic Joint Effusion, Michael E. Siegel ... (Jun) 709

#### Obstetrics and Gynecology:

Avoiding Pregnancy in Isotretinoin Users, Ron E. Swensen .. (Apr) 406
An Ovarian Cancer Tumor Marker, CA 125, Comes of Age, Richard E. Buller, Philip J. DiSaia ... (Apr) 406
Drug Therapy for Genital Herpes, Paul A. Hensleigh ... (Apr) 407
β-Streptococcal Cultures in Obstetrics, R. Harold Holbrook, Jr ... (Apr) 407
Estrogen Hormone Replacement to Minimize Cardiovascular Risk, L. Michael Kettel ... (Apr) 408
Gonadotropin-Releasing Hormone Agonist Treatment of Endometriosis and Myomas, Linda C. Giudice ... (Apr) 409
Endometrial Ablation, Arnold Kresch ... (Apr) 409
Medical Treatment of Ectopic Pregnancy, Amin A. Milki, Jamshid Moossazadeh ... (Apr) 410
New Therapies for Genital Warts, David A. Grimes ... (Apr) 410
Laparoscopic Surgery for Ectopic Pregnancy, G. David Adamson ... (Apr) 411
Therapeutic Insemination by Donor, Lee R. Hickok ... (Apr) 411
Update on α-Fetoprotein Screening in California, George Cunningham ... (Apr) 412
Testing for Chlamydial Infection, A. Eugene Washington ... (Apr) 413

#### Occupational Medicine:

Electromagnetic Field Exposure and Risks of Cancer in Children, Ellen B. Gold ... (Feb) 172
Isocyanates, Polyurethane Paints, and Asthma, John Balmes, Stephanie J. London, John M. Peters ... (Feb) 172
Health Hazards of Occupational Diesel Exhaust Exposure, Marc B. Schenker ... (Feb) 173
Health Hazards of Radon Exposure, Jonathan M. Samet ... (Feb) 174
Male Reproductive Toxicity, William Daniell ... (Feb) 174
Ethylene Oxide Carcinogenicity, Charles E. Becker ... (Feb) 175
Occupational Back Pain of Nurses, Philip Harber ... (Feb) 175
Occupational Liver Disease, Carrie A. Redlich ... (Feb) 176

#### Preventive Medicine and Public Health:

Advances in Prenatal Screening, Theodore G. Ganiats, David M. Baughan ... (Mar) 285
Correspondence, Berthold E. Umland ... (Jun) 721
Medication Misuse in the Elderly, Philip G. Weiler ... (Mar) 286
Pesticides in Food, Richard J. Jackson, Anna M. Fan ... (Mar) 286
The Epidemic of Childhood Drowning, Sylvia H. Micik, Janice Yuwiler ... (Mar) 287
Injuries—The 'Neglected Disease of Modern Society,' Sylvia H. Micik, Janice Yuwiler ... (Mar) 288
The Preventive Use of Zidovudine in Asymptomatic HIV Infection, Michael S. Gottlieb ... (Mar) 288
Preventing Lead Poisoning in Children, Lynn R. Goldman, Robert D. Schlag, Mary Haan, Kenneth W. Kizer ... (Mar) 289
The Tuberculosis and HIV Connection, Le Quoc Hanh, Paul T. Davidson ... (Mar) 290
Opportunities for Preventing Woman Abuse and Battering, Ivy Schwartz ... (Mar) 290

#### Radiology:

Color Doppler Ultrasonography of the Liver, Edward G. Grant ... (Jan) 62
Endovaginal Ultrasonography, Frankin N. Tessler ... (Jan) 62
Percutaneous Cholecystostomy for Acute Cholecystitis, John P. McGahan ... (Jan) 63
Gadolinium in Magnetic Resonance Imaging of the Central Nervous System, Anton N. Hasso ... (Jan) 63

Magnetic Resonance Imaging for Diagnosing Avascular Necrosis of Bone, Tamara Miner Haygood, Michael R. Williamson, Robert Rosenberg ..... (Jan) 64
Biliary Lithotripsy, Eric vanSonnenberg, Horacio D'Agostino, Giovanna Casola, Alan F. Hofmann ..... (Jan) 64
Percutaneous Management of Common Bile Duct Calculi, Jeffrey C. Brandon, Larry-Stuart Deutsch ..... (Jan) 65
Transrectal Ultrasonography and Biopsy, Dennis A. Sarti .... (Jan) 65
Magnetic Resonance Imaging for Staging Head and Neck Cancer, Bradley A. Jabour, Robert A. Lufkin, William N. Hanafee. (Jan) 66

Erythrocytosis Caused by an Erythropoietin-Producing Breast Adenocarcinoma, Robert F. Bohnen, Mussa Banisadre, Rolf N. Gulbrandson, Esmail D. Zanjani ..... (Apr) 417
Espresso Maker's Wrist (Correspondence), Dennis Shusterman ..... (Jun) 721
Evaluation of Hematuria in Adults (Topics in Primary Care Medicine), Douglas C. Bauer ..... (Mar) 305
Expert Systems in Treating Substance Abuse (Addiction Medicine), Donald R. Wesson, Robert H. Hink ..... (May) 585
Eye of the Beholder (Correspondence), Gerard N. Burrow .. (Apr) 427

## F

Family Practice Training in California, see *Future of*
Fasciitis, see *Tryptophan Use and*
Fatal Pulmonary Infection With *Mycobacterium fortuitum*, Joseph Nussbaum, P. N. R. Heseltine ..... (Apr) 423
Fetal Tissue in Transplantation, see *Policy Concerning the Therapeutic Use of Human*
Fleeting Moments (Lessons From the Practice), Kirsti A. Dyer ..... (Feb) 195
Future of Family Practice Training in California (Informed Opinion), John E. Midtling, Paul G. Barnett, H. John Blossom, William H. Burnett ..... (Mar) 317

## G

*Giardia lamblia*, see *Serum Antibodies to*
*Giardia*-Specific Antibodies, see *Biological Significance of*

## H

Head and Neck, see *Mohs' Micrographic Surgery of the*
Health Care—Where Are the Problems and Where Are the Solutions? (Editorial) ..... (Jan) 68
Correspondence, Ira E. Bailie ..... (Apr) 429
Health Care Allocation—The Continuing Oregon Experiment, see *Developing Principles for Prudent*

### Health Care Delivery:

Health Care Needs and Services for Technology-Dependent Children in Development Centers, Lucy S. Crain, Donald N. Mangravite, Robert Allport, Marianne Schour, Krist Biakanja ..... (Apr) 434
Low-Birth-Weight Effects of Demographic and Socioeconomic Variables and Prenatal Care in Pima County, Arizona, Ivy L. Schwartz ..... (Jun) 725

Health Care Needs and Services for Technology-Dependent Children in Developmental Centers (Health Care Delivery), Lucy S. Crain, Donald N. Mangravite, Robert Allport, Marianne Schour, Krist Biakanja ..... (Apr) 434
Health Quackery Use Among Patients—A Physician Survey, see *Perceived*
Hematuria in Adults, see *Evaluation of*
Herpes Zoster Phrenic Neuritis With Respiratory Failure, William L. Melcher, Robert A. Dietrich, Warren L. Whitlock ..... (Feb) 192
High-Dose Epinephrine Therapy and Other Advances in Treating Cardiac Arrest (Medical Staff Conference), Discussant: Michael L. Callaham ..... (Jun) 697
Hilar Mass Without Pulmonary Disease, see *Left*
HIV Epidemic, see *Physician Risk and Responsibility in the*
Human Fetal Tissue in Transplantation, see *Policy Concerning the Therapeutic Use of*
[Human Immunodeficiency Virus], see *Integration of Prevention Efforts*
Human Immunodeficiency Virus Antibody Testing, see *Confidential Versus Anonymous*
Human T-Lymphotropic Virus Type I (HTLV-I) and Tropical Spastic Paraparesis or HTLV-I-Associated Myelopathy in Hawaii, Peter S. Dixon, Anne J. Bodner, Michael Okihiro, Andrea Milbourne, Arwind Diwan, Jeffrey M. Nakamura (Mar) 261
Hypertension, see *Long-Acting Nifedipine Versus Metoprolol as Monotherapy for Essential*
Hypertension in the Elderly, see *Perspective on*
Hypocalcemia, see *Low Intracellular Magnesium in Patients With Acute Pancreatitis and*
Hypoplastic Left-Sided Heart Syndrome, see *Neonatal Cardiac Allotransplantation Facilitated by In Utero Diagnosis of*
Hypotension, Catecholamines, and α-Adrenergic Receptors in Mitral Valve Prolapse, see *Orthostatic*

## I

Iatrogenic Illness (Correspondence), Terence M. Davidson .. (Apr) 426
Immunotherapy for Infectious Diseases (Medical Staff Conference), Discussant: James E. Pennington ..... (Apr) 401
Immunotherapy for Malignant Melanoma, see *Acute Pancreatitis Associated With High-Dose Interleukin-2*
Impaired Physicians, see *Diversion Programs for*
Infectious Disease?, see *Peptic Ulcer—An*
Infectious Diseases, see *Immunotherapy for*

### Information:

Perceived Health Quackery Use Among Patients—A Physician Survey, Robin Nishiwaki, Alice Morton, Carla Bouchard, James A. Peters, William T. Jarvis ..... (Jan) 87
Simplified Screening Test for the Diagnosis of Allergy, A. Ali Imam, Harold S. Novey, H. Alice Orgel, Gerald L. Klein, Eli O. Meltzer, Robert W. Ziering ..... (Mar) 313
Sleep Deprivation and Cognitive Testing in Internal Medicine House Staff, John Robbins, Fred Gottlieb ..... (Jan) 82

### Informed Opinion:

Future of Family Practice Training in California, John E. Midtling, Paul G. Barnett, H. John Blossom, William H. Burnett... (Mar) 317

Integration of Prevention Efforts (Correspondence), Kenneth W. Kizer, James A. Felten, Vaughn A. Jodar, Hiroshi E. Yamamoto, Jean M. Montes ..... (Apr) 428
Interleukin-2 Immunotherapy for Malignant Melanoma, see *Acute Pancreatitis Associated With High-Dose*
Internal Medicine House Staff, see *Sleep Deprivation and Cognitive Testing in*

### In the Forefront:

Developing Principles for Prudent Health Care Allocation—The Continuing Oregon Experiment, Ralph Crawshaw ..... (Apr) 441

Intracellular Magnesium in Patients With Acute Pancreatitis and Hypocalcemia, see *Low*
Intracranial Tuberculoma Developing During Therapy for Tuberculous Meningitis, Joseph L. Malone, Scott Paparello, Leland S. Rickman, Kenneth F. Wagner, Brian Monahan, Edward C. Oldfield ..... (Feb) 188
In Utero Diagnosis of Hypoplastic Left-Sided Heart Syndrome, see *Neonatal Cardiac Allotransplantation Facilitated by*
Is It Fair to Blame the Victim? (Correspondence), Arthur D. Silk ..... (Feb) 186

## K

Kaposi's Sarcoma, see *Chylothorax and Respiratory Failure in*
Kidney Transplant Revisited (1990) (Editorial), William J. C. Amend, Jr ..... (Jun) 711

## L

Left Hilar Mass Without Pulmonary Disease (Radiologic Case), Mark G. Stephens, Jonathan M. Levy ..... (Jan) 93

### Lessons From the Practice:

After Shock, Mark Renneker ..... (Jan) 90
Bernstein's Hug, Elliott B. Oppenheim ..... (Feb) 196
Fleeting Moments, Kirsti A. Dyer ..... (Feb) 195
My Favorite Patients Are on Medicaid, Joseph E. Scherger... (Jan) 92
Trivia Champ and Honorary Faculty Member, William B. Shore ..... (Apr) 449
Two Generations—Reflections on Changes in the Treatment of a Chronic Disease, Lucy M. Osborn ..... (Mar) 322

Life-Style and Illness (Correspondence), Ira E. Bailie ..... (Apr) 429

Listerial Brain Abscess, see *Successful Medical Treatment of*
Long-Acting Nifedipine Versus Metoprolol as Monotherapy for Essential Hypertension—A Randomized Controlled Crossover Study, Kam S. Woo, Chiu O. Pun ..... (Feb) 149
Low-Birth-Weight Effects of Demographic and Socioeconomic Variables and Prenatal Care in Pima County, Arizona (Health Care Delivery), Ivy L. Schwartz ..... (Jun) 725
Low Intracellular Magnesium in Patients With Acute Pancreatitis and Hypocalcemia (Clinical Investigation), Elisabeth Ryzen, Robert K. Rude ..... (Feb) 145

## M

Magnesium in Patients With Acute Pancreatitis and Hypocalcemia, see *Low Intracellular*
Malignant Melanoma, see *Acute Pancreatitis Associated With High-Dose Interleukin-2 Immunotherapy for*
Malpractice Litigation as a Factor in Choosing a Medical Specialty (Medical Practice), Charlene E. Pyskoty, Thomas E. Byrne, Sara C. Charles, Kevin J. Franke ..... (Mar) 309
Medicaid, see *My Favorite Patients Are on*

### Medical Ethics:

Policy Concerning the Therapeutic Use of Human Fetal Tissue in Transplantation, Robert M. Nelson ..... (Apr) 447

### Medical Practice:

Malpractice Litigation as a Factor in Choosing a Medical Specialty, Charlene E. Pyskoty, Thomas E. Byrne, Sara C. Charles, Kevin J. Franke ..... (Mar) 309

### Medical Progress:

Amnestic Disorders—Pathophysiology and Patterns of Memory Dysfunction, Kenneth R. Erickson ..... (Feb) 159
Editorial, Arthur P. Shimamura ..... (Feb) 177
Bone Marrow Transplantation, Part II—Autologous, Nelson J. Chao, Karl G. Blume ..... (Jan) 46
Chronic Urticaria, Barbara A. Burrall, Georges M. Halpern, Arthur C. Huntley ..... (Mar) 268
Editorial, Stephen I. Wasserman ..... (Mar) 292
Current Status of Renal Transplantation, Michael G. Suranyi, Bruce M. Hall ..... (Jun) 687
Editorial, William J. C. Amend, Jr ..... (Jun) 711
Perspective on Hypertension in the Elderly, Barbara Whitcomb, Richard L. Byyny ..... (Apr) 392
Editorial, William McFate Smith ..... (Apr) 414

Medical Specialty, see *Malpractice Litigation as a Factor in Choosing*

### Medical Staff Conferences:

High-Dose Epinephrine Therapy and Other Advances in Treating Cardiac Arrest, Discussant: Michael L. Callaham ..... (Jun) 697
Immunotherapy for Infectious Diseases, Discussant: James E. Pennington ..... (Apr) 401
Peptic Ulcer—An Infectious Disease?, Discussant: Walter L. Peterson ..... (Feb) 167
Physician Payment Reform—An Idea Whose Time Has Come, Discussant: Philip R. Lee ..... (Mar) 277
Physician Risk and Responsibility in the HIV Epidemic, Discussant: Molly Cooke ..... (Jan) 57
Correspondence, Jeoffry B. Gordon ..... (Jun) 723

Medical Therapeutics, see *N-of-1 Clinical Trials—A Technique for Improving*
Medicine in Extraordinary Times (Editorial) ..... (Jun) 711

### Medicine in Perspective:

Trench Foot—A Study in Military-Medical Responsiveness in the Great War, 1914-1918, John S. Haller, Jr ..... (Jun) 729

### Medicine in Society:

Who Are You, Doc?, Gary G. Kardos ..... (Jan) 95

Memory and Amnesia (Editorial), Arthur P. Shimamura .... (Feb) 177
Memory Dysfunction, see *Amnestic Disorders*
Meningitis, see *Intracranial Tuberculoma Developing During Therapy for Tuberculous*
Methadone Maintenance in the Treatment of Opioid Dependence (Addiction Medicine), Joan Ellen Zweben, J. Thomas Payte ..... (May) 588
Metoprolol as Monotherapy for Essential Hypertension, see *Long-Acting Nifedipine Versus*
Military-Medical Responsiveness in the Great War, 1914-1918, see *Trench Foot—A Study in*
Misdiagnosing Ventricular Tachycardia in Patients With Underlying Conduction Disease and Similar Sinus and Tachycardia Morphologies (Clinical Investigation), Blair D. Halperin, Jack Kron, Joel E. Cutler, Peter J. Kudenchuk, John H. McAnulty ..... (Jun) 677
Mitral Valve Prolapse, see *Orthostatic Hypotension, Catecholamines, and α-Adrenergic Receptors in*
Mohs' Micrographic Surgery of the Head and Neck (Clinical Review), Gary L. Darmstadt, Howard K. Steinman ..... (Feb) 153
Correspondence, Richard E. Safrin ..... (Jun) 722
Monotherapy for Essential Hypertension, see *Long-Acting Nifedipine Versus Metoprolol as*
*Mycobacterium fortuitum*, see *Fatal Pulmonary Infection*
Myelopathy in Hawaii, see *Human T-Lymphotropic Virus Type I (HTLV-I) and Tropical Spastic Paraparesis or HTLV-I-Associated*
My Favorite Patients Are on Medicaid (Lessons From the Practice), Joseph E. Scherger ..... (Jan) 92

## N

National Health Insurance in America—The Issue of Copayment (Correspondence), Janos Balog ..... (Jan) 76
Neonatal Cardiac Allotransplantation Facilitated by In Utero Diagnosis of Hypoplastic Left-Sided Heart Syndrome, Joyce Johnston, Elmar P. Sakala, The Loma Linda University Heart Transplant Group ..... (Jan) 70
Neonates, see *Drug-Exposed*
Neuritis With Respiratory Failure, see *Herpes Zoster Phrenic*
Neuromas, see *Acoustic*
New Disease Model of Alcoholism (Addiction Medicine), John Wallace ..... (May) 502
Nicotine Dependence, and Treatment, see *Cigarette Smoking,*
Nifedipine Versus Metoprolol as Monotherapy for Essential Hypertension, see *Long-Acting*
N-of-1 Clinical Trials—A Technique for Improving Medical Therapeutics (Specialty Conference), Discussant: Eric B. Larson ..... (Jan) 52
Editorial, Gordon H. Guyatt ..... (Jan) 67
Noonan's Syndrome in a Female Infant With Spontaneous Resolution of Cystic Hygroma and Hydrops, see *Prenatal Diagnosis of*
Nuclear Medicine, see *Epitomes*

## O

Obstetrics and Gynecology, see *Epitomes*
Occupational Illness and Poison Control Centers—Referral Patterns and Service Needs (Public Health and Preventive Medicine), Paul D. Blanc, Neil Maizlish, Patricia Hiatt, Kent R. Olson, David Rempel ..... (Feb) 181
Editorial, Toby L. Litovitz, J. Douglas White ..... (Feb) 178
Occupational Medicine, see *Epitomes*
Opiates, see *Drugs of Abuse*
Opioid Dependence, see *Methadone Maintenance in the Treatment of*
Oregon Experiment, see *Health Care Allocation*
Orthostatic Hypotension, Catecholamines, and α-Adrenergic Receptors in Mitral Valve Prolapse (Clinical Investigation), Irwin J. Schatz, Subramanyam Ramanathan, Rosie Villagomez, Charles MacLean ..... (Jan) 37

## P

Pancreatitis and Hypocalcemia, see *Low Intracellular Magnesium in Patients With Acute*
Pancreatitis Associated With High-Dose Interleukin-2 Immunotherapy for Malignant Melanoma, see *Acute*
Parenteral Nutrition Use at a University Hospital—Factors Associated With Inappropriate Use, Steven J. Katz, Robert K. Oye ..... (Jun) 683
Pathologist's View of Mohs' Micrographic Surgery (Correspondence), Richard E. Safrin ..... (Jun) 722
Patients' Presence in Prenatal Screening (Correspondence), Berthold E. Umland ..... (Jun) 721
Peptic Ulcer—An Infectious Disease? (Medical Staff Conference), Discussant: Walter L. Peterson ..... (Feb) 167
Perceived Health Quackery Use Among Patients—A Physician Survey (Information), Robin Nishiwaki, Alice Morton, Carla Bouchard, James A. Peters, William T. Jarvis ..... (Jan) 87

Perinatal Addiction, see *Treatment of*
Perspective on Hypertension in the Elderly (Medical Progress), Barbara Whitcomb, Richard L. Byyny ..... (Apr) 392
Editorial, William McFate Smith ..... (Apr) 414
Pharmacologic Approaches to the Treatment of Cocaine Dependence (Addiction Medicine), Wanda A. Taylor, Mark S. Gold ..... (May) 573
Phrenic Neuritis With Respiratory Failure, see *Herpes Zoster*
Physical Diagnosis Versus Modern Technology—A Review, Faith T. Fitzgerald ..... (Apr) 377
Physician Payment Reform—An Idea Whose Time Has Come (Medical Staff Conference), Discussant: Philip R. Lee ... (Mar) 277
Physician Risk and Responsibility in the HIV Epidemic (Medical Staff Conference), Discussant: Molly Cooke ..... (Jan) 57
Correspondence, Jeoffry B. Gordon ..... (Jun) 723
Physicians as Role Models in Society (Editorial) ..... (Mar) 292
Physician's Guide to Discontinuing Benzodiazepine Therapy (Addiction Medicine), Robert L. DuPont ..... (May) 600
Plasma Cell Dyscrasia, Polyneuropathy, and Diabetes Mellitus, see *Syndrome of*
Pneumomediastinum With Substance Abuse, see *Association of Spontaneous*
Poison Control Centers—Referral Patterns and Service Needs, see *Occupational Illness and*
Policy Concerning the Therapeutic Use of Human Fetal Tissue in Transplantation (Medical Ethics), Robert M. Nelson ..... (Apr) 447
Polyneuropathy, and Diabetes Mellitus, see *Syndrome of Plasma Cell Dyscrasia,*
Pregnancy, see *Electroconvulsive Therapy Use During*
Pregnancy Hazard Alert, see *Vitamin A*
Prenatal Care in Pima County, Arizona, see *Low-Birth-Weight Effects of Demographic and Socioeconomic Variables and*
Prenatal Diagnosis of Noonan's Syndrome in a Female Infant With Spontaneous Resolution of Cystic Hygroma and Hydrops, Luis Izquierdo, Ori Kushnir, Diane Sanchez, Luis Curet, Patricia Olney, Gloria E. Sarto, Carol Clericuzio, Richard Olney ..... (Apr) 418
Prenatal Screening, see *Patients' Presence in*
Prescription Drug Abuse—Patient, Physician, and Cultural Responsibilities (Addiction Medicine), Donald R. Wesson, David E. Smith ..... (May) 613
Prescription Drugs, see *Abuse of*
Preventive Medicine and Public Health, see *Epitomes*
Primary Care for AIDS and Chemical Dependence (Addiction Medicine), Lori D. Karan ..... (May) 538
Primary Care Physician, see *Addiction Medicine*
Psychiatric Disorders, and AIDS, see *Drug Abuse,*

**Public Health and Preventive Medicine:**

Occupational Illness and Poison Control Centers—Referral Patterns and Service Needs, Paul D. Blanc, Neil Maizlish, Patricia Hiatt, Kent R. Olson, David Rempel ..... (Feb) 181
Editorial, Toby L. Litovitz, J. Douglas White ..... (Feb) 178
Vitamin A—A Pregnancy Hazard Alert, Kenneth W. Kizer, Anna M. Fan, Jolanta Bankowska, Richard J. Jackson, Donald O. Lyman ..... (Jan) 78
Editorial, Edward Lammer ..... (Jan) 67

Pulmonary Complications of Smoked Substance Abuse (Addiction Medicine), Donald P. Tashkin ..... (May) 525
Pulmonary Disease, see *Left Hilar Mass Without*
Pulmonary Infection With *Mycobacterium fortuitum,* see *Fatal*
Pulsatile Mass of the Left Tympanic Membrane, see *36-Year-Old Woman With a*
Putting Practice Into Law (Correspondence), Jeoffry B. Gordon ..... (Jun) 723
Pyomyostitis of the Abdominal Wall Musculature Mimicking Acute Abdomen, see *Tropical*

## Q

Quackery Use Among Patients—A Physician Survey, see *Perceived Health*

## R

**Radiologic Case:**

Left Hilar Mass Without Pulmonary Disease, Mark G. Stephens, Jonathan M. Levy ..... (Jan) 93
36-Year-Old Woman With a Pulsatile Mass of the Left Tympanic Membrane, Jody Reiser, Kelvin S. Danielson, Jonathan M. Levy, Richard D. Zonis, Fred K. Christensen ..... (Apr) 439

Radiology, see *Epitomes*
Renal Transplantation, see *Current Status of*
Respiratory Failure, see *Herpes Zoster Phrenic Neuritis With*
Respiratory Failure in Kaposi's Sarcoma, see *Chylothorax and*
Rhabdomyolysis and *Staphylococcus aureus* Septicemia in a Man With the Acquired Immunodeficiency Syndrome, Albert W. Wu, Kurt Benirschke, J. Allen McCutchan ..... (Jun) 716
Risk and Responsibility in the HIV Epidemic, see *Physician*
Role of Physicians as Medical Review Officers in Workplace Drug Testing Programs—In Pursuit of the Last Nanogram (Addiction Medicine), H. Westley Clark ..... (May) 514
Ruminations of an Aspiring Californian (Correspondence), Albert W. Wu, Haya R. Rubin ..... (Jun) 722

## S

Sensory Loss, see *Capgras's Syndrome Associated With*
Serum Antibodies to *Giardia lamblia* by Age in Populations in Colorado and Thailand, Edward N. Janoff, David N. Taylor, Peter Echeverria, Mary P. Glode, Martin J. Blaser ..... (Mar) 253
Editorial, Martin F. Heyworth ..... (Mar) 293
Serum Cholesterol and Apolipoprotein Fractions in Human Subjects, see *Effect of Chromium Picolinate on*
[Sexually Transmitted Diseases], see *Integration of Prevention Efforts*
Sideroblastic Anemia, see *Zinc Abuse—An Unsuspected Cause of*
Simplified Screening Test for the Diagnosis of Allergy (Information), A. Ali Imam, Harold S. Novey, H. Alice Orgel, Gerald L. Klein, Eli O. Meltzer, Robert W. Ziering ..... (Mar) 313
Sinus and Tachycardia Morphologies, see *Misdiagnosing Ventricular Tachycardia in Patients With Underlying Conduction Disease and Similar*
Sleep Deprivation and Cognitive Testing in Internal Medicine House Staff (Information), John Robbins, Fred Gottlieb ... (Jan) 82
Smoking, Nicotine Dependence, and Treatment, see *Cigarette*
Socioeconomic Variables and Prenatal Care in Pima County, Arizona, see *Low-Birth-Weight Effects of Demographic and*

**Special Editorials:**

Tribute to Malcolm S. M. Watts, MD,
Dwight L. Wilbur ..... (Jun) 735
Lloyd H. Smith, Jr ..... (Jun) 735
Linda Hawes Clever ..... (Jun) 736

**Specialty Conference:**

N-of-1 Clinical Trials—A Technique for Improving Medical Therapeutics, Discussant: Eric B. Larson ..... (Jan) 52
Editoral, Gordon H. Guyatt ..... (Jan) 67

*Staphylococcus aureus* Septicemia in a Man With the Acquired Immunodeficiency Syndrome, see *Rhabdomyolysis and*
Substance Abuse, see *Association of Spontaneous Pneumomediastinum With*
Substance Abuse, see *Expert Systems in Treating*
Substance Abuse, see *Pulmonary Complications of Smoked*
Successful Medical Treatment of Listerial Brain Abscess, Wanda S. Updike, Cynthia J. Anderson, Max S. Lundberg, Spotswood L. Spruance ..... (Mar) 298
Surgery of the Head and Neck, see *Mohs' Micrographic*
Syndrome of Plasma Cell Dyscrasia, Polyneuropathy, and Diabetes Mellitus, Michael L. Davies, David L. Elson, Dwight Hertz, J. Michael McMillin ..... (Mar) 257

## T

Tachycardia Morphologies, see *Misdiagnosing Ventricular Tachycardia in Patients With Underlying Conduction Disease and Similar Sinus and*
Technology-Dependent Children in Developmental Centers, see *Health Care Needs and Services for*
36-Year-Old Woman With a Pulsatile Mass of the Left Tympanic Membrane (Radiologic Case), Jody Reiser, Kelvin S. Danielson, Jonathan M. Levy, Richard D. Zonis, Fred K. Christensen (Apr) 439
Three Possible Futures for Medicine (Editorial) ..... (Apr) 414
Thymic Carcinoid and Multiple Endocrine Neoplasia (Correspondence), Douglas W. Blayney ..... (Apr) 426
Thymus, see *Carcinoid Tumors*

**Topics in Primary Care Medicine:**

Dupuytren's Disease, Steven M. Gonzalez, Richard I. Gonzalez ..... (Apr) 430
Evaluation of Hematuria in Adults, Douglas C. Bauer ..... (Mar) 305

Transplantation, see *Current Status of Renal*
Transplantation, see *Policy Concerning the Therapeutic Use of Human Fetal Tissue*
Transplant Revisited (1990), see *Kidney*
Treatment of Perinatal Addiction—Identification, Intervention, and Advocacy (Addiction Medicine), Marty Jessup . . . . . (May) 553
Trench Foot—A Study in Military-Medical Responsiveness in the Great War, 1914-1918 (Medicine in Perspective), John S. Haller, Jr . . . . . (Jun) 729
Tribute to Malcolm S. M. Watts, MD, (Special Editorials),
Dwight L. Wilbur . . . . . (Jun) 735
Lloyd H. Smith, Jr . . . . . (Jun) 735
Linda Hawes Clever . . . . . (Jun) 736
Trivia Champ and Honorary Faculty Member (Lessons From the Practice) . . . . . (Apr) 449
Tropical Pyomyositis of the Abdominal Wall Musculature Mimicking Acute Abdomen, Charles A. Kennedy, Glenn Mathisen, Matthew B. Goetz . . . . . (Mar) 296
Tropical Spastic Paraparesis or HTLV-I-Associated Myelopathy in Hawaii, see *Human T-Lymphotropic Virus Type I (HTLV-I) and*
Trust (Correspondence), Louis Borgenicht . . . . . (Feb) 185
Tryptophan Use and Fasciitis (Correspondence),
Bruce T. Adornato, Yuan Chang, Dikran Horoupian, Maie Herrick, Elaine Lambert, George V. Lawry, Martin Stein . . . . . (Apr) 427
Tumors of the Thymus, see *Carcinoid*
Tuberculous Meningitis, see *Intracranial Tuberculoma Developing During Therapy for*
Two Generations—Reflections on Changes in the Treatment of a Chronic Disease (Lessons From the Practice), Lucy M. Osborn . . . . . (Mar) 322
Tympanic Membrane, see *36-Year-Old Woman With a Pulsatile Mass of the Left*

## U

Ulcer—An Infectious Disease?, see *Peptic*
University Hospital, see *Parenteral Nutrition*
Urticaria, see *Chronic*

## V

Ventricular Tachycardia in Patients With Underlying Conduction Disease and Similar Sinus and Tachycardia Morphologies, see *Misdiagnosing*
Vitamin A—A Pregnancy Hazard Alert (Public Health and Preventive Medicine), Kenneth W. Kizer, Anna M. Fan, Jolanta Bankowska, Richard J. Jackson, Donald O. Lyman . (Jan) 78
Editorial, Edward Lammer . . . . . (Jan) 67

## W

War on Drugs (Correspondence), R. Lawrence Gibson . . . . . (Mar) 427
Watts, Malcolm S. M., see *Tribute to*
Who Are You, Doc? (Medicine in Society), Gary G. Kardos . (Jan) 95
Wolff-Parkinson-White Syndrome, see *Current Management of the*

## Z

Zinc Abuse—An Unsuspected Cause of Sideroblastic Anemia, Walter B. Forman, Denice Sheehan, Susan Cappelli, Bryon Coffman . . . . . (Feb) 190
Correspondence, H. A. Ronaghy . . . . . (Jun) 723

# Classified Advertisements

The rate for each insertion is **$7 per line** (average six words per line) **with five lines ($35) minimum.** Confidential box number charge: $5 each month.

**Classified display rates $50 per inch. Maximum sizes: 1 column by 10 inches or 2 columns by 5 inches. Larger classified ad space by special arrangements.**

Copy for classified advertisements should be received not later than **25th of the second month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. Although The Western Journal of Medicine believes the classified advertisements in these columns to be from reputable sources, we do not investigate the offers made and assume no liability concerning them. The right is reserved to reject, withdraw, or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

**Please Type or Print Advertising Copy**

## Classified Advertisements Are Payable in Advance

CLASSIFIED ADVERTISEMENTS
THE WESTERN JOURNAL OF MEDICINE
P.O. BOX 7602, SAN FRANCISCO, CA 94120-7602
(415) 541-0900, ext. 376

### CALIFORNIA

Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Jim Ellis, Director, (415) 673-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (818) 999-1050 or (800) 635-3175.**

**PHYSICIAN OPPORTUNITIES IN ARIZONA.** Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 90 plus physicians in Tucson, Green Valley, and Tempe, Arizona, has positions available in these cities in Internal Medicine, Pediatrics, OB/GYN, Orthopedics, Urgent Care, and Family Practice. Excellent fringe benefits and profit sharing program. Fee-for-service, as well as owned HMO. Must be BE/BC. Call or write James J. Vitali, CEO, Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732; (602) 322-8300.

**INTERNAL MEDICINE.** Long established multispecialty group in central Washington needs Internist. Independent contract or join partnership later. University town with many cultural and recreational activities. Send CV to Medical Building Associates, 200 E. 6th, Ellensburg, WA 98926, or call (509) 925-9891.

**GYNECOLOGIST** needed for 78-bed JCAHO hospital. We are growing and we need to enlarge our specialty staff. Just opened new Cancer Treatment Center. 12,000 community, 90,000 immediate service area, 160,000 catchment area. Great outdoors area, cattle, oil, gas, hunting, fishing, good schools, low crime, ideal area for raising children. Reasonable malpractice rates. Send CV to Marilyn Bryan, Community Hospital, PO Box 2339, Elk City, OK 73648: (405) 225-2511.

**BC/BE NORTHWESTERN CALIFORNIA.** OB/GYN needed to join the oldest office in the Redwood area on the North Coast. An excellent opportunity for a male or female, American trained physician. Excellent compensation and incentive program leading to corporate membership in one year. Three physicians in office but only two doing Obstetrics. Send CV and references to T. W. Loring, MD or W. C. Weiderman, MD, 2607 Harris St, Eureka, CA 95501; (707) 442-4593.

### Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services
5414 E. Montecito, Fresno, CA 93727
Or call 1 (800) 873-0786

**NORTHERN CALIFORNIA.** The Permanente Medical Group, Inc, has immediate openings for BC/BE General Internists at the Roseville facility. Kaiser Permanente is a leader in health care, providing quality medical care to a rapidly growing population. We offer a tremendous benefit package and starting salary for career oriented physicians. Roseville is a foothill community located 90 miles from San Francisco and 100 miles from Lake Tahoe and Sierra skiing. University affiliation and teaching appointments are available. Send CV to Tony Cantelmi, MD, The Permanente Medical Group, Inc, 1001 Riverside Blvd, Roseville, CA 95678. EOE.

**RADIOLOGIST.** Part-time position available immediately in small hospital with general radiography and fluoroscopy, mammography and ultrasound in Weaverville, California. Contact Drs Wheeler, Biggs, or Babbitt, West Coast Radiology, 3798 Janes Rd, Ste 12, Arcata, CA 95521; office number (707) 822-3621, ext 191.

### SOUTHERN CALIFORNIA

Specialists and Primary Care Physicians—CIGNA Healthplans invites you to join our innovative and dynamic managed health care team. Our multidisciplinary HMO practice provides a supportive and collegial work environment at 31 locations. You will enjoy a wealth of cultural and recreational activities, access to major academic centers, and an excellent compensation package. *Call collect* **(818) 500-6570 or send CV to Robert Harrington, MD, Professional Recruitment, CIGNA Healthplans of California, 505 N. Brand Blvd, Ste 400-49, Glendale, CA 91203.**

### HSI RESOURCES DIV

Health Services Inc

HEALTHCARE PERSONNEL SERVICES

HSI currently has numerous opportunities in California and Washington state for qualified physicians and Orthopedic Surgeons. These positions offer:

- Flexible hours and days.
- No on-call or mandatory weekends.
- Competitive salary plus bonus plan.
- Paid vacation, sick, holiday, and CME.
- 401 K retirement savings programs with matching contributions.
- Full medical/dental.
- Relocation assistance.
- Strict confidentiality.
- All fees paid by employer.

Call
**Jeannette Bezemer**
collect or write:
**HSI RESOURCES**
**2600 Michelson Dr, #1130**
**Irvine, CA 92715**
**(714) 476-9163**

**SAN FRANCISCO BAY AREA** multispecialty group seeks Pediatrician BC/BE, to join 26 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Daniel Rowe, MD, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

**OREGON.** Family Practice opportunity in sunny southern Oregon. Three physicians seeking two associates, so bring a colleague! No Obstetrics. Great quality of life. Contact Mark Wood, Klamath Family Practice, (503) 883-8134.

**CENTRAL CALIFORNIA.** Join our team of Family Practice Physicians in a progressive community health center near Fresno, California. Competitive salary with extra on-call and overtime. Malpractice paid. Generous vacations and time-off policy. Affiliated with UCSF with on-site Family Practice residents and medical students. Varied practice, including Obstetrics, Pediatrics, and in-patient care with an emphasis on health maintenance, patient education, and primary care research. Position is 60 percent clinical, 40 percent teaching. Bilingual English-Spanish helpful. Contact Ardeth Bier, Fresno County Dept of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3353.

**URGENT CARE/PRIMARY CARE PHYSICIANS** for over 90 positions available with various physician groups in Phoenix metropolitan/Tucson, Arizona. Excellent compensation and partnership opportunities. Contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

**HAWAII.** Family Practitioner needed for rural underserved area. Full-time position in nonprofit community health clinic. No OB, hospitalizations optional. Desire dedicated person to work in multicultural setting. Contact Alan Chun, MD, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-7081.

*(Continued on Page 748)*

(Continued from Page 747)

PHYSICIANS WANTED

**Longview** is a picturesque, stable community of 42,000 located near the Columbia Gorge and the coastal mountains and beaches of Washington and Oregon. Members of our 12-physician group enjoy individual subpractices, infrequent call, and new state-of-the-art medical offices.

We invite you to contact us at the above address regarding practice opportunities. Or call Judy Parmenter, Physician Recruitment, (503) 280-2050 for further information.

**BC/BE CARDIOLOGIST FULL-TIME.** Community hospital in San Mateo, California. Mark L. Highman, MD, (415) 573-3786.

**RADIOLOGIST FOR SOUTHEASTERN UTAH.** Excellent practice opportunity to join second Radiologist. Primary service area of 30,000 people with 88-bed community hospital. Nuclear, CT, mammography, ultrasound, and radiography. Contact Milton Bauermeister, MD, Castleview Hospital, Price, UT 84501; (801) 637-4800, ext 280 or (801) 472-5403.

**OB/GYN, INTERNISTS,** Family Practitioners, Pediatricians for Arizona and western opportunities. Quality positions available other regions of country. Inquiries confidential. Mitchell & Associates, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

**GENERAL INTERNIST.** Multispecialty group located in San Luis Obispo, California, seeks a BC/BE physician. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to Physician Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

**FAMILY PRACTITIONER.** Multispecialty group located in San Luis Obispo, California, seeks a BC/BE physician. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to Physician Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

## PHYSICIANS
## REGISTERED
## PHYSICAL THERAPISTS
## PHYSICIAN ASSISTANT

Currently seeking California/Nevada state licensed BC/BE physicians and other medical professionals to perform Workers' Compensation and Personal Injury treatment and evaluation in our many California and Nevada locations. Spanish speaking a plus. Specialties include Neurology, Orthopedic, Internal Medicine, Psychiatry, Plastic Surgery, Occupational Medicine, Industrial Medicine.

We offer:

- Full-time or part-time
- Flexible hours
- Guaranteed income
- Possible expense for relocation
- Will provide training
- Excellent growth potential

Contact 1 (800) 347-2821

**INTERNIST, PEDIATRICIAN** to join multispecialty group. Salary with incentive, early partnership. Northern California. Reply to Number 197, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**OB/GYN.** Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

**CALIFORNIA, SANTA CLARA COUNTY.** Positions currently available for experienced physicians to provide primary care services at hospital based Urgent Care Center in San Jose. Minimum guarantee of $100,000 plus annual for 42-hour work week, 48 weeks per year with paid malpractice. No night call. Please contact Nanette Peter, Associated Emergency Physicians, Inc, Medical Group of Northern California, 1625 The Alameda, Ste 201, San Jose, CA 95126; (408) 293-8881.

**MULTIPLE FAMILY PRACTICE** (BC/BE) positions available in several suburban satellite clinics of a large Seattle area multispecialty group practice. Diverse patient population includes managed care, fee-for-service, and retired military (at some satellite clinics). Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

**MD TO ASSIST** in busy Orthopedic clinic and Operating Room. Will also take call. Position has been used in the past as a bridge to Orthopedic residency. Attractive salary and excellent benefit package. Washington State licensure required. Available immediately. Send CV or contact Mary Anderson, Personnel Representative, Pacific Medical Center, 1200-12th Ave S., Seattle, WA 98144; (206) 326-4111.

**FAMILY PRACTITIONER, INTERNIST, PEDIATRICIAN** BC/BE for thriving community clinic in ideal southern California climate. Modern facility, planned expansion. Call is optional, flexible scheduling. Diverse population includes working poor, managed care, 50 percent Hispanic; presents opportunities for interesting community medicine. Malpractice covered, competitive salary. Escondido Community Clinic, Tracy Ream, Executive Director, 401 N. Spruce St, Escondido, CA 92025; (619) 747-1867.

**CALIFORNIA MULTISPECIALTY.** Cardiologist, Internal Medicine, Pediatrician, Endocrinologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist, Dermatologist, Ophthalmologist, General Surgeon, Podiatrist. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center—5, 17821 S. Pioneer Blvd, Artesia, CA 90701.

PHYSICIANS WANTED

## PHYSICIANS NEEDED

The continuing growth of our service area population (now 90,000) has created an immediate need for additional BC/BE physicians in the following specialities:

- **NEUROLOGY.** Establish private practice with no investment, guaranteed income. Proficiency in EEG, EMG required.
- **GENERAL/THDRACIC SURGERY.** Establish private practice in General and Thoracic Surgery (no open heart) with no investment, guaranteed income.
- **ONCOLDGY.** Establish private practice with no investment, guaranteed income. Some General Internal Medicine necessary initially.
- **ORTHDPEDIC SURGERY.** No investment, guaranteed income. Above average earning potential.
- **RADIOLOGY.** Hospital group position. Excellent salary and benefit package. Competency in ultrasound, CAT, Nuclear Medicine, film screen mammography, and general diagnosis required. MRI experience desired. Inpatient and outpatient. (California license is required.)

112-bed full service hospital, very well equipped. Excellent ancillary services. Our service area population is now 90,000; a growing area with new businesses and a stable economy.

Located in central California near Sequoia National Park, Tulare offers an excellent family oriented life-style and all expected amenities. Beautiful homes, close to hospital and office, are affordably priced. Good schools, many community activities, and abundant recreation including golf, tennis, skiing, mountain and equestrian activities. Easy access to all California's major metropolitan and resort areas.

Contact:

**Tulare District Hospital Physician Recruiting Office, PO Box 90112, Los Angeles, CA 90009; (213) 216-2687.**

**OCCUPATIONAL MEDICINE PHYSICIAN.** BC is preferred, but will consider physician with a strong background in Occupational Medicine. Competitive salary and benefits. Located in an outstanding community, the Santa Clarita Valley. If you would like to continue to use your clinical skills, yet also be involved in administrative decisions, please submit your CV to Richard Kessler, Dir., Occup. Health Services, c/o SCV Healthcare Management Group, Valencia, CA 91355.

**SAN FRANCISCO BAY AREA.** BE/BC Internist. We currently are seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 prepaid Health Plan members. Recently renovated and expanded medical center facilities are within convenient communting distance to virtually any bay area city and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to Winslow Wong, MD, Attn: Administration, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545. EOE.

**PEDIATRICIANS, BC/BE** to join busy, well established Pediatric practice in San Francisco suburb. Two Pediatricians looking for two full-/part-time associates to replace two retiring partners. Guaranteed salary leading to early partnership. Flexible hours possible. Large patient base means you can be busy from first day. Excellent hospitals with neonatal and pediatric ICUs. University appointments possible. Beautiful San Francisco bay area convenient to ski areas, beaches, wine country. Gerald Harris, MD, Pediatric Medical Group, 1800 Sullivan Ave, Ste 507, Daly City, CA 94015; (415) 756-5150.

(Continued on Page 749)

# We've Put Life-Saving Technology In The Right Hands.

At FHP, providing quality health care is our number one priority. Because this commitment is so vital to us, we've put this challenging responsibility in the most capable hands around. Then we make sure they have everything they need to perform at their highest level.

As one of our valued Physicians, you'll experience all the benefits that come from working with one of the nation's largest and most progressive HMOs. You'll work with dedicated colleagues in every discipline with a wide range of advanced health care equipment at your disposal. Perhaps the greatest benefit is the professional freedom you'll enjoy. We've alleviated many of the headaches of private practice while providing a predictable work schedule and fully-paid malpractice insurance.

This new found freedom will give you more time to enjoy all the benefits of our attractive locations in Southern California, Arizona, New Mexico, Utah and Guam. No matter what your personal desires, FHP has a location to satisfy them.

Get your hands on a rewarding career with FHP. Call us toll free at 800-336-2255 (in CA) or 800-446-2255 (outside CA). Or send your CV/resume to: FHP, Professional Staffing, Dept. 99, 9900 Talbert Avenue, Fountain Valley, CA 92708. Equal Opportunity Employer.

A graduate of Washington University and the New Jersey School of Medicine, Neonatologist Eugene L. Mahmoud, M.D., joined FHP in July of 1989. Dr. Mahmoud completed his fellowship at the University of California at San Diego in Neonatology and is currently on staff at FHP Hospital's Level II NICU unit.

Giving Physicians More Of What They Want

FHP HEALTH CARE


*(Continued from Page 748)*

## PHYSICIANS WANTED

**CALIFORNIA AND WESTERN STATES**
Opportunities for BE/BC physicians in metropolitan and rural areas in Cardiology, Critical Care, Emergency Medicine, Endocrinology, ENT, Family, Internal Medicine, Neurology, Neurosurgery, OB/GYN, Orthopedics, Pediatrics, Pulmonology, Rheumatology, and Urology. **Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.**

**STD FELLOWSHIP.** One-year training program: clinical and epidemiologic aspects of sexually transmitted diseases. Available immediately. Jointly sponsored by UCSF/SF Department of Public Health. Send inquiries with CV to Infectious Diseases, SF General Hospital, 995 Potrero St, San Francisco, CA 94110. EO/AA employer M/F.

**CRITICAL CARE MEDICINE.** Four MDs BC both Internal Medicine and Critical Care Medicine seeking fifth associate with similar credentials in busy Critical Care Medicine practice. Central California City, over 500,000 population. Reply to Number 207, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**OB/GYN,** Internist, Family Practitioner, Pediatrician, Orthopedist, Industrial Medicine Practitioner, and others. BC/BE. Fast growing community in beautiful San Joaquin Valley, close to Sierras, ocean, and metropolitan Los Angeles. Cost of living very reasonable. Unique opportunity to enter own private practice, associated with a medical center without the hassle of being an employer. A single lease fee and fee-for-service provides you private office, fully equipped exam rooms, nursing staff, receptionist, billing, accounting and insurance specialist, and housekeeping. Also on premises available for your use, are surgery facilities, x-ray, and laboratory. Send CV or call Sequoia Medical Management Group, 3800 Niles, Ste #2, Bakersfield, CA 93306; (805) 398-2041.

## PHYSICIANS WANTED

**SAN FRANCISCO BAY AREA,** General Internist. Energetic BC/BE General Internist needed immediately for nine MD Fremont satellite of Palo Alto Medical Clinic. Broad inpatient/outpatient Internal Medicine practice in growing bay area community. Excellent location for family with convenient access to San Francisco. Please send CV to David Hooper, MD, PAMC, Fremont Center, 39500 Liberty St, Fremont, CA 94538.

**BC/BE FAMILY PRACTICE or GENERAL INTERNIST** sought to join established private practices seeking expansion in Pacific Beach, La Jolla, and Clairemont areas of San Diego. Must be sensitive and humanitarian. Income guarantee and partnership available for right individual. Women encouraged to apply. Please send CV to J. Simmons, Mission Bay Hospital, 3030 Bunker Hill St, San Diego, CA 92109.

**DIRECTOR OF EMERGENCY MEDICINE.** Immediate opening for Director-Emergency Medicine. Salary plus incentives. Present volume, 6,000 visits annually. Please contact Mike R. Piper, Churchill Community Hospital, Fallon, NV; (702) 423-3151.

**EUGENE CLINIC, EUGENE, OREGON**
Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Family Practice, Geriatrics, Occupational Medicine, Orthopedics, Psychiatry, Urgency Care, Urology. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

**Physician Recruiter**
**1162 Willamette St**
**Eugene, OR 97401**

## PHYSICIANS WANTED

**PHYSICIAN OPPORTUNITIES NATIONWIDE**
For all specialities for hospitals, clinics, multispecialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists. **Nugent & Grant, Inc, 1400 Coleman, Ste B-22, Santa Clara, CA 95090; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

**ALBUQUERQUE, NEW MEXICO.** BC/BE Family Practitioners sought to join established, private practice, single specialty group practice. Income guarantee, benefits. Please send CV to Kathryn Rhoades, Presbyterian Healthcare Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 6330.

**BC/BE INTERNAL MEDICINE** physician for Primary Care group practice in growing Fresno Community. Well orchestrated/staffed office with associated lab. Contact Michael W. Lynch, MD, 5151 N. Palm, Ste 200, Fresno, CA 93704; (209) 229-2786.

**CALIFORNIA, MOTHER LODE COUNTRY.** Family Practice, General Practice, in rural community health center. Excellent recreation area. Send CV or contact Randy Windsor, Executive Director, PO Box 897, Pioneer, CA 95666; (209) 295-5544.

**FAMILY PRACTICE OPPORTUNITY.** Association available in rural town, one hour from Seattle and one-half hour from Tacoma, Obstetrics optional. Growing community close to mountains and Puget Sound. Owner to retire in four to five years. (206) 829-1444.

**MD, BC/BE** in Occupational Medicine, Internal Medicine, Family Practice, or ER to join established free-standing Occupational Medicine clinic. Attractive opportunity for growth. Competitive salary and benefits. Send CV to Manager, MBI Industrial Medicine, Inc, 2539 N. 35th Ave, Phoenix, AZ 85009.

*(Continued on Page 750)*

(Continued from Page 749)


# WASHINGTON STATE
## ROCKWOOD CLINIC, PS

An expanding 70 physician multispecialty fee-for-service group seeks BC/BE physicians in the following specialties:

| | |
|---|---|
| ALLERGY | OCCUPATIONAL MEDICINE |
| CARDIOLOGY | HEMATOLOGY/ONCOLOGY |
| DERMATOLOGY | OB/GYN |
| INTERNAL MEDICINE | RHEUMATOLOGY |
| PEDIATRICS | GENERAL SURGERY |
| FAMILY PRACTICE | ORTHOPEDICS |

Attractive benefit package includes competitive salary leading to early shareholder status.

CONTACT: **Colleen Mooney, Recruitment Coordinator**
**Rockwood Clinic, PS**
**E. 400 Fifth Ave**
**Spokane, WA 99202**
**(509) 838-2531**

**COME ENJOY SPOKANE'S QUALITY LIFE-STYLE!**

KAISER PERMANENTE
*Good People. Good Medicine*

## NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

SMA Southwest Medical Associates
A Sierra Health Services Company

## ENDOCRINOLOGIST / NEUROLOGIST

An opportunity is waiting for you with Nevada's oldest and largest multi-specialty Group Practice. We have immediate openings for highly qualified physicians in the specializations of Endocrinology and Neurology.

Las Vegas has a rapidly growing (750,000 +) population, mild climate, affordable housing, no state income tax, plus abundant recreational and cultural activities.

Excellent compensation and benefits package including:
- **401K • Stock option plan • Paid malpractice • C.M.E.**
- **Relocation expenses**

*If you are interested in an exciting and financially rewarding opportunity in a progressive health care organization, please forward your C.V. to: Janet R. Bishop, Manager, Physician Recruitment, Southwest Medical Associates, P.O. Box 15645, Las Vegas, NV 89114-5645.*

## CALIFORNIA, COLORADO OR UTAH YOUR CHOICE

There are private practice opportunities now available in the following Humana California, Colorado and Utah communities:

**ORANGE COUNTY, CA**
**NEUROSURGEON**—Opportunity to establish private practice in west Ordnge County and also provide coverage at a Neurotrauma Receiving Center at our 182-bed hospital. Financial assistance and a patient base will come from our three Orange County hospitals and fast-developing health care plan.

**DENVER**
**FAMILY PHYSICIANS**—Several group and associate opportunities, for both M.D.'s and D.O.'s, now exist in the suburbs of Aurora and Thornton.

**LAYTON, UTAH**
**FAMILY PHYSICIANS**—Associate needed to join young, board-certified Family Physician in newly opened office. Layton is 12 miles south of Ogden and 15 miles north of Salt Lake City.

For other opportunities in these states, send your CV to: Gordon Crawford, Manager, Professional Relations, Humana Inc., Dept. HH-6, 500 West Main Street, Louisville, KY 40201-1438. Or call TOLL-FREE 1-800-626-1590.

Humana®


(Continued on Page 751)

(Continued from Page 750)


# PHYSICIANS

## PRIMARY CARE

### CALIFORNIA

JSA, Inc. is currently offering physicians full, part-time, and PRN positions in Primary Care Clinics located in San Diego and Sacramento.

**BENEFITS PACKAGE**

- **Flexible day-time hours**
- **No "on-call" requirement**
- **Malpractice insurance reimbursement**
- **Professional development funding**
- **Incentive programs**
- **Exceptional salary level**

**QUALIFICATIONS**

- **BC or graduate of an approved residency program in a Primary Care Specialty**
- **MD or DO**
- **Current state licensure**
- **ACLS/BCLS**

A proposed project in Oceanside includes positions in Emergency Medicine and Primary Care Specialties.

For further information, please contact Susan Bray, Recruiting Director at (301) 964-2811. JSA, Inc., PO Box 1305, Columbia, MD 21044.

JSA

HEALTHCARE

Consulting - Management - Services

An Equal Opportunity Employer

# Join us.

**PACIFIC NORTHWEST**
**Group Health Cooperative of Puget Sound**

One of the nation's largest and oldest HMOs currently has permanent and locum tenens positions available for:

Family Practitioners
Pediatricians
Physician Assistants
Psychiatrist–General
Psychiatrist–Child
Psychologist

To inquire, write:
Manager, Medical Staff Personnel
Group Health Cooperative of Puget Sound
521 Wall Street
Seattle, WA 98121

or call (206) 448-6546

# THE PERMANENTE MEDICAL GROUP
# NORTHERN CALIFORNIA

QUALITY

STABILITY

LEADERSHIP

GROWTH

SUPPORT

REWARDS

The Permanente Medical Group, the largest multispecialty group practice in the U.S., is undergoing explosive growth in its Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley. Our rapid increase in membership has created practice opportunities throughout the region.

Our physician-managed group is part of the comprehensive Kaiser Permanente Medical Care Program. As a TPMG physician, you have access to the latest medical technology and resources, the support of colleagues in all subspecialties — and the opportunity to provide excellent health care without the burdens of managing a practice.

TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, continuing education, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. For complete information, call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-7153, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800) 777-4912. EOE

KAISER PERMANENTE
*Good People. Good Medicine.*


(Continued on Page 752)

(Continued from Page 751)

## CALIFORNIA
### FAMILY PRACTICE
### INTERNAL MEDICINE
### SURGEON and PEDIATRIC

physicians to join Family Walk-In Medical Centers staff, a growing health care provider with five medical centers in Fresno, California, which is located in the Central San Joaquin Valley. Fresno metropolitan area has a population of over 400,000. Easy access to major metropolitan areas, Pacific coast and the Sierras. Salary guarantee of $100K to $120K for Family Practice, Internal Medicine, and Pediatric physicians; $150K for Surgeons, or equal to an average of the last two years' earnings, whichever is greater. Malpractice paid. Excellent working conditions. Contact **Juanita Perry, Human Resources Director, Family Walk-In Medical Centers, 1021 E. Herndon Ave, Fresno, CA 93710; (209) 449-6430**

**NORTHERN CALIFORNIA—SAN FRANCISCO BAY AREA.** Leading HMO is seeking BC/BE physician to staff a busy urban, full-service Emergency Department with the possibility of administrative advancement. Kaiser Permanente is a large prepaid HMO offering competitive salary, job security, shareholder status, and generous benefits including health care, life insurance, disability insurance, sick leave, mortgage assistance, and educational leave. Please address all inquiries to David Witt, MD, Emergency Dept, Kaiser Permanente Medical Center, 1200 El Camino Real, South San Francisco, CA 94080-3299; or call (415) 742-2516. EOE.

**SAN FRANCISCO NORTH BAY AREA/NAPA VALLEY.** Immediate openings (career and part-time) in a multidiscipline Emergency Department for physicians trained in Emergency Medicine, Internal Medicine, Family Practice, or Pediatrics. Full in-house multispecialty coverage. Complete generous benefit package. Contact Robert Mack, MD, Kaiser Hospital, 975 Sereno Dr, Dept WJM, Vallejo, CA 94589; (707) 648-6200. EOE.

**FAMILY PRACTITIONER, FORT COLLINS, COLORADO.** Excellent opportunity to join well established solo practitioner in beautiful, choice, front range city 60 miles north of Denver, Colorado. Modern spacious office within walking distance of hospital. For further information and details call 1 (303) 224-9900, or write to Medical Business Office, 419 Canyon Ave, Ste #220, Fort Collins, CO 80521.

**ORTHOPEDIC SURGEON.** BC Orthopedic Surgeon needed for office practice in beautiful southern California area. Full- or part-time, surgery optional. Excellent compensation package. Send CV to Ronald Gilbert, MD, c/o Gilbert Medical Group, 1076 E. First St, #A, Tustin, CA 92680; or call (714) 832-1516.

**NEAR STANFORD.** Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

**CALIFORNIA—NORTHERN.** Area's leading private practice group has immediate and future positions for BC/BE Family Practice and Primary Care Physicians in its Department of Ambulatory Care and General Medicine. Excellent compensation, incentive program, full benefits, early equity position, retirement plan. Experience life-style and professional fulfillment in beautiful northern California. Call Maureen Forrester: (408) 282-7833. Send CV to San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112.

**NORTHERN CALIFORNIA.** Multispecialty group in central valley community 60 miles east of San Francisco seeks well-trained OB/GYN, Cardiologist, ENT, Pediatrician, and Neurologist. Growing community 32,000 in rural-suburban setting offers reasonable housing costs, good schools, and nearby recreational areas. Ken Baker, PSG, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

**SOUTHERN CALIFORNIA.** Young Family Practitioner with dynamic practice seeking associate for future partnership. Generous salary/guarantee and incentives package. New medical office near outstanding 300-bed community hospital. Growing community within one hour of beaches and mountains. Ken Baker, PSG, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

**FAMILY PRACTICE PHYSICIAN.** Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

**WENATCHEE, WASHINGTON, PACIFIC NORTHWEST.** Wenatchee Valley Clinic, a 95-physician multispecialty clinic, is seeking a BC/BE General Internist. Guaranteed first year salary, incentive production bonus available. Attractive fringe benefit package. Located on the Columbia River in the sunny eastern foothills of the Cascades. Abundant recreational activities available. Send résumés to Wenatchee Valley Clinic, PO Box 489, Wenatchee, WA 98807, Attn: Julie Zimmerman.

## EXCELLENT
## FAMILY PRACTICE
### OPPORTUNITY

ROCKWOOD CLINIC, P.S.—a network of Family Practice clinics (main building and six satellites) seeks BE/BC Family Practitioners to join these busy independent practices offering the full range of inpatient/outpatient services, including obstetrics. ADVANTAGES INCLUDE:

- Join the largest department within this multispecialty group (15 Family Practitioners)
- Immediate in-house specialty consultation
- Well trained administrative support to assist in business matters, while allowing autonomy regarding the decisions of your practice
- Attractive benefit package includes excellent salary leading to early shareholder status

SPOKANE, WASHINGTON (metropolitan population 350,000), offers very affordable housing, unlimited year-round recreation, excellent schools, and numerous cultural organizations.

CONTACT:
**Colleen Mooney**
**Recruitment Coordinator**
**Rockwood Clinic**
**E. 400 Fifth Ave**
**Spokane, WA 99202**
**(509) 838-2531**

## GROWING, ESTABLISHED (1923)

35 physician multispecialty medical group with four locations in northeast central San Fernando Valley (north section of the Los Angeles City and County) seeks 1990/1991 BC/BE California licensed physicians in the following specialties:

INTERNAL MEDICINE
FAMILY PRACTICE
PEDIATRICS
OB/GYN
GENERAL SURGERY

Qualified candidates please send CV and references to:

**Mr Donald Abramsky, MBA**
**Administrator**
**Facey Medical Group, Inc.**
**11211 Sepulveda Blvd**
**Mission Hills, CA 91345-1196**
**(818) 365-9531**

**OB/GYN.** BC/BE to join 20 physician (OB, Pediatrics, Internal Medicine) practice in sunny central Washington. Reasonable call schedule with three OB/GYN department. Competitive salary, excellent benefit package including vacation at 30 days per year and professional liability. Contact Ann Garza, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

**ORTHOPAEDIC SURGEON.** Outstanding opportunity to join seven extremely busy Orthopaedic Surgeons and one Physiatrist in private practice. The practice site is located in a major city in the western United States. Completion of a spinal fellowship is mandatory. A highly competitive guaranteed income and benefit package will be provided. Contact Bob Suleski, 250 Regency Ct, Waukesha, WI 53186; 1 (800) 338-7107.

**INTERNAL MEDICINE.** BC/BE Internist. Excellent practice opportunity for General Internist. Located midway between Sacramento and San Francisco serving a rapidly growing community with a population of 70,000 plus. Office space in close proximity to new community hospital. Extremely attractive assistance package available. For further information please call or write Gary Stein, MD, 501 Nut Tree Ct, Vacaville, CA 95687; (707) 446-7100.

**AMBULATORY CARE,** Hayward and Modesto. Thriving practices, attractive facilities. Competitive salary, profit-sharing, partnership, growth potential, paid malpractice. Contact Jane Dressler, California Emergency Physicians, 2101 Webster St, #1050, Oakland, CA 94612; (415) 835-7431 or, (800) 842-2619 outside of California.

**STAFF PHYSICIAN.** Join us in providing comprehensive medical care for 330 developmentally disabled children and adults at the Wyoming State Training school. Three physicians and one physician's assistant staff our 18-bed health care center and provide medical support to nursing, therapists, professional and paraprofessional staff across campus. Good working relationships with excellent hospital and medical group in local community. Progressive habilitation-oriented working environment. Attractive benefits, malpractice insurance provided, no overhead. Annual salary range $50,000 to $70,000 depending upon experience and qualifications. Campus situated in pleasant west-central Wyoming community of Lander, minutes from beautiful Wind River Mountain Range and close to Yellowstone and Grand Teton National Parks. Outstanding hiking, fishing, hunting, skiing, wilderness areas nearby. Good schools and services, low cost of living, no state income tax. Contact Director of Clinical Services, Wyoming State Training School, 8204 State Highway 789, Lander, WY 82520; or call (307) 332-5302. Equal Opportunity Employer.

(Continued on Page 753)

(Continued from Page 752)

## PHYSICIANS WANTED

**The DEPARTMENT of PEDIATRIC HEMATOLOGY/ONCOLOGY at VALLEY CHILDREN'S HOSPITAL**

is seeking a second, full-time hospital-based Pediatric Hematologist/Oncologist. The candidate must be BC or BE in Pediatric Hematology/Oncology. Responsibilities include patient care, teaching, and clinical research.

Valley Children's Hospital is affiliated with the Children's Cancer Study Group and with the University of California, San Francisco, Fresno Pediatric Residency Program.

Please contact:

**Stan Schofield**
**Assistant Vice President**
**Medical Affairs,**
**Valley Children's Hospital**
**3151 N. Millbrook**
**Fresno, CA 93703**

**STUDENT HEALTH PHYSICIAN**

No night calls, no weekend duties, summers free, no Medi-Cal. BC/BE Family Physician being sought immediately by

**Student Health Center**
**Cal State University, Stanislaus**
**Turlock, CA 95380.**

For details call
**Personnel Office**
**(209) 667-3351 or (209) 667-3177.**

**SOUTHERN CALIFORNIA.** 39,000 visit Emergency Department in new hospital in San Bernardino. Base station and separate fast track with opportunity to teach. Opening for director and career Emergency Physicians at $90 per hour. Chance to join prestigious, democratic, academically oriented emergency group with excellent benefits. Contact Art Wong, MD, FACEP, Emergency Physicians Medical Group, 120 Montgomery St, San Francisco, CA 94104; (415) 989-1242.

**CALIFORNIA, NORTHERN.** A stable group of four ABEM certified/elgible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klamath, Rogue, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1000, San Francisco, CA 94104.

**SAN FRANCISCO BAY AREA.** Pain management practice. Excellent staff and administration. Opportunity for Internist, Psychiatrist, Family Practitioner, Neurologist, or partnership interested in pain or psychosomatic medicine. Reply to Number 208, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**ARIZONA.** BC/BE Hematologist/Oncologist to join expanding multispecialty group with established referral network. Ideal northwestern Arizona location. Competitive salary and benefits. Send CV/call Eddie Arnold, Administrator, Mohave Valley Medical Center, 1225 E. Hancock, Bullhead City, AZ 86442; 1 (602) 758-3931.

**MARYSVILLE (YUBA CITY).** Primary care provider. Northern California primary care clinic with large Medi-Cal clientele. Three physicians, two physician assistants. No OB. No surgery. Near mountains, close to Sacramento, 2½ hours to Lake Tahoe and San Francisco. Salary $86,113 plus. Please contact Ed Allen, 938 14th St, Marysville, CA 95901; or call (916) 741-6244.

## POSITIONS AVAILABLE

**FAMILY NURSE PRACTITIONER**

Three residency trained BC Family Practitioners seek a Family Nurse Practitioner to join their community health center practice. Located on the eastern slopes of the Sierras in northeastern California. Practice entails full scope of Family Practice. Excellent opportunity for recreation in local mountains including fishing, hiking, bicycling, camping, water-skiing, wind-surfing, sailing and in winter, both downhill and cross-country skiing. Includes a complete benefit package, malpractice coverage, health insurance, vacation, CME, etc. Salary commensurate with experience. Staff includes two Family Nurse Practitioners, one physician assistant, clinical psychologist, registered dietician, health educators, biofeedback therapist, and prenatal instructors. If interested send CV to **NRHC, Inc, 1306 Riverside Dr, Susanville, CA 96130, Attn: Paul W. Holmes, MD, Medical Director; or call (916) 257-7849**

## PRACTICES AVAILABLE

**SAN DIEGO COUNTY.** Cardiology, Internal, OB/GYN and Pediatric practices available. Long established—doctors retiring. Various prices and low down payments. Call CBI, San Diego County's professional practice sales specialists, (619) 283-7009.

**CORONA, SOUTHERN CALIFORNIA.** Great opportunity to take over a busy established Internal Medical/Pulmonary Disease practice. Good coverage. Excellent income. Negotiable terms. Reply to Number 199, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**SANTA CLARA.** General Practice MD retiring after 42 years of practice. No Medi-Cal. US trained MDs only. Fully equipped office. Location one mile from Valley Fair Shopping Mall and two miles from O'Connor Hospital, San Jose. Call Dr Dow H. Ransom, (408) 243-8722 or (408) 867-4892.

**NORTHERN CALIFORNIA.** Urgent and Routine Care Clinic. Currently limited as a one physician operation. Large patient base. 2,600 square feet. Fully equipped and computerized. Collecting $265K. Country setting. Reply to Number 205, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**SOUTHERN CALIFORNIA** inland empire. Fastest growing area in state. General practice 35 years, no OB. Good 325-bed hospital. Good exchange call group every sixth weekend. Will introduce. Terms: reply to Number 203, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

## PRACTICE SALE

**NORTHERN AND CENTRAL CALIFORNIA**

Established practices available. Dermatology, Family, Internal Medicine, OB/GYN, Ophthalmology, Otolaryngology, Pediatrics, Plastic Surgery, and Urology. Reasonable terms and prices. Call/write **Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.**

**FAMILY PRACTICE, BERKELEY, CALIFORNIA.** Growing established practice in beautiful San Francisco bay area shared with one associate. Modest buy-in. (415) 843-4544.

**CALIFORNIA RADIOLOGY.** Well established Diagnostic Radiology practice is available in Sacramento. General and mammography. Annual collections $550,000 plus. Call or write John Harrison, Practice Dynamics, 11222 Richmond, Ste 125, Houston, TX 77082; 1 (800) 933-0911.

**FAMILY PRACTICE AVAILABLE.** Napa Valley, California, premier Family Practice, BC, established 20 plus years. Highest reputation. Excellent hospital two blocks, plus call coverage. Office two suite building owned by seller, purchase option possible. Will introduce. CV/inquires to V. Bouillon, MD, 3030 Beard Rd, Napa, CA 94558.

**INTERNAL MEDICINE**—San Diego City, high development area. Gross $160,000. Low overhead with high net cash flow. Contact Practice Consultants. (619) 528-2321, Dr Bernard Press, Broker.

**SAN DIEGO NORTH COUNTY.** Ambulatory Care Family Practice/Occupational Medical Center. Gross $475,000. Well located, attractive, fully equipped 2,700 square foot office. Open 8:00 am to 8:00 pm, 7 days per week. Contact Practice Consultants, Dr Bernard Press, Broker, (619) 528-2321.

**FOR SALE.** Well established practice in Plastic and Reconstructive Surgery with full equipment for major and minor procedures in office. Located in south Orange County, California. Surgeon retiring. Open staff in local hospitals. Reply to Number 209, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

**INTERNAL MEDICINE.** Practice available, Prescott, Arizona. A fine group of regular patients. Excellent living, facilities, coverage. Call for details (602) 445-2335 after 6 pm. Expanding territory.

**DON'T FORGET!**

The deadline for submitting classifieds for the August issue of WJM is June 25. Send your advertisement to

**Classified Advertising**
**WJM, PO Box 7602**
**San Francisco, CA 94120-7602**

## COURSES

**FOURTH INTERNATIONAL WORKSHOP ON FUTURE DIRECTIONS IN INTERVENTIONAL CARDIDLOGY.** September 7-9, 1990. Santa Barbara, California. Fees: $365 for ACC members; $430 for non-members; $220 for residents, fellows-in-training, nurses, and technicians. 21.5 Category 1 credit hours. For information, call **American College of Cardiology, (800) 253-4636, in Maryland (301) 897-5400, ext 228.**

**THE FOURTEENTH ANNUAL SEMINAR: CARDIOLOGY UPDATE 1990.** October 18-20, 1990. Carmel, California. Fees: $410 for ACC members; $480 for non-members. 11 Category 1 credit hours. For information, call **American College of Cardiology, (800) 253-4636; in Maryland, (301) 897-5400, ext. 228.**

(Continued on Page 754)

(Continued from Page 753)

**GROWTH AREA OF SANTA CLARA VALLEY.** New medical office space for lease in the growth area of Silicon Valley, Morgan Hill, California. Easy access, abundant parking, well located, generous tenant improvement allowances. Excellent patient referral sources. Contact Dr Jon Hatakeyama, (408) 779-7391.

**IRVINE.** Office available for lease July 1, 1990. Woodbridge Medical Center. Four exams, two consults, large business office. Fully equipped, all equipment for sale as is. (714) 857-0575.

**WESTERN PHYSICIANS REGISTRY**
**Locum Tenens Service**
**Permanent Placement**

Since 1980, WPR has served the needs of California's physicians. When someone needs coverage or ongoing, part-time help, we find the right physician. When a practice must expand, we find a permanent associate. We pride ourselves on our discretion, our very personal service matching the right person with the right job. We work only in California, concentrating our efforts where we know our market. Our clients include private practices, HMOs, urgent care centers, emergency departments, multispecialty groups, and community clinics.

**Northern California**
**Jim Ellis, Director**
**(415) 673-7676 or (800) 437-7676**

**Southern California**
**Tracy Zweig, Director**
**(818) 999-1050 or (800) 635-3175**

**LOCUM TENENS INFORMATION**

**PHYSICIANS**
**& OPPORTUNITIES**
**AVAILABLE**
**CALL 1-800-531-1122**

**SOUTHERN CALIFORNIA.** Beautiful waterfront property in the Ventura keys. Custom home with boat dock, in a professional neighborhood. Adjacent to the Ventura harbor and marina. Call Jack Finnegan (805) 648-5915.

*Ads Get Results!*
**CLASSIFIED ADVERTISING INFORMATION**
**(415) 541-0900, Ext 376**

**$5,000-$60,000 FOR PHYSICIANS.** Unsecured signature loans for any need including taxes, debts, investments, etc. No points or fees. Best rates. Level payments up to six years—no prepayment penalty. Call toll free 1 (800) 331-4952, Medi-Versal Department 114.

**EARN 12 PERCENT PLUS**

Secured by real estate or real estate mortgages.

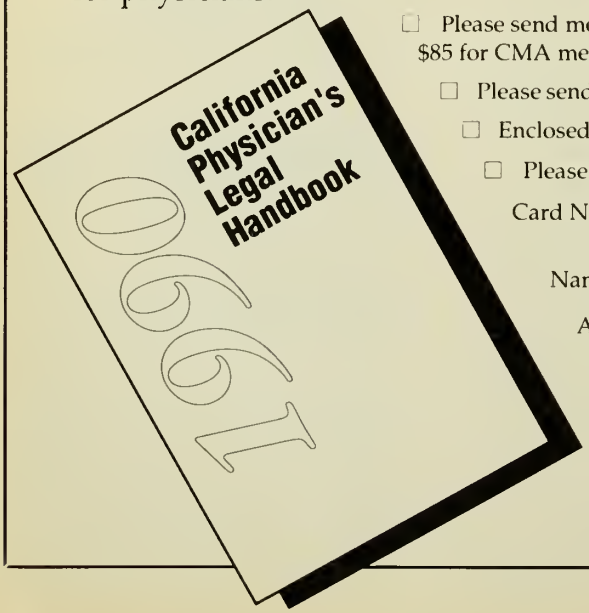
- Title Company insured!
- Under 65 percent of appraisal
- Independent collection agent
- Management included!

**CALL JACK W. HILTON**
**(602) 375-8951**
**10640 N. 28th Dr, #C-205**
**Phoenix, AZ 85029**

**AT LAST!** Western Practitioner Resources places nurse practitioners, physician assistants, and certified nurse midwives in your clinical setting. Please phone Heidi Bourne, Director, (800) 345-5859 or (707) 839-5859.

# AVOID LITIGATION: KNOW THE LAWS PERTAINING TO YOUR PRACTICE

The *California Physician's Legal Handbook* is **the** legal guide for California physicians. Written by CMA Legal Counsel, this 600 page handbook costs much less than an hour of an attorney's time, and can save you thousands of dollars in attorneys' fees. A **must** for physicians.




☐ Please send me a copy of the 1990 *California Physician's Legal Handbook*. $85 for CMA members; $185 for non-members. Prices include tax and shipping.

☐ Please send me more information on the CPLH.

☐ Enclosed is my check or money order.

☐ Please charge my ☐ VISA or ☐ Mastercard

Card No. _____ Exp. _____

Name _____

Address _____

City, State, Zip _____

Phone number ( _____ ) _____

Mail to, or call: Sutter Publications, Inc.,
P.O. Box 7690, San Francisco, CA 94120-7690
(415) 882-5175

The Western Journal of Medicine

SINCE 1902 • CIRCULATION 56,000+

# Classified Advertisements

The rate for each insertion is **$7 per line** (average six words per line) **with five line ($35) minimum.** A confidential box number (in lieu of your address) can be assigned to your advertisement for $5 each month. The replies to the box number will be directly forwarded to you as they arrive at *WJM*'s office.

**Classified display rates $50 per inch. Maximum sizes: 1 column by 10 inches or 2 columns by 5 inches. Larger classified ad space by special arrangements.**

Copy for classified advertisements should be received not later than **25th of the second month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

**Please Type or Print Advertising Copy**

## Classified Advertisements Are Payable in Advance

THE WESTERN JOURNAL OF MEDICINE
P.O. BOX 7602, SAN FRANCISCO, CA 94120-7602
(415) 541-0900 EXT. 376

# ad copy

Print or Type Clearly

Number of lines _____ × $7 = $_____

Optional: Confidential box number charge: +$5 = _____

**Subtotal (minimum $35 *or* minimum $40 with confidential box number)** $_____

Number of insertions _____ × $_____ = (subtotal)

**Check enclosed for:** $_____

Name (Please Print)

Contact

Address

City/State/Zip

(_____)_____
Phone

Signature

SOMETHING TO THINK ABOUT...

# THE PRACTICE, THE PATIENTS, THE PRESCRIPTIONS ARE YOURS.

KEEP THE PRESCRIBING DECISION YOURS, TOO.

SPECIFY: DISPENSE AS WRITTEN

VALIUM®
brand of
diazepam/Roche IV

The cut out "V" design is a registered trademark of Roche Products Inc.

scored tablets

YOUR CHOICE ALL ALONG!

ROCHE®
Roche Products

Roche Products Inc.
Manati, Puerto Rico 00701

Copyright © 1989 by Roche Products Inc. All rights reserved